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'Duracillin, in Oil'

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Original Communications

RESPIRATORY ACIDOSIS AND ALKALOSIS IN CHILDREN

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DISTURBANCES of acid-base balance are associated with numerous disorders of infancy and childhood, and acidosis or alkalosis may account for much of the symptomatology which a patient presents. Restoration to normal of acid-base relationships may be a necessary part of the treatment of seemingly unrelated diseases.

We have been impressed by the incidence in childhood of respiratory acidosis and alkalosis, conditions well defined by the chemist and physiologist but all too often not recognized by the clinician.[1] To clarify the relationships of respiratory acidosis and alkalosis to other types of acid-base disturbances in infancy and childhood, a brief review of the control of the chemical reaction of body fluids may be helpful.

The chemical reaction of fluids in the body may be influenced by the absorption of nutriment and fluids from the gastrointestinal tract; the losses of water, electrolytes, and tissue waste products through the kidneys; losses of water and carbon dioxide through the lungs; and the losses of water, electrolytes, and waste products through the skin. Uptake or loss through these organs affects the composition of blood plasma and, secondarily, of the interstitial fluids. The chemical conditions within the body cells must then be mediated through exchange of metabolic materials between the cells and the surrounding extracellular fluids. The environment of the cells is of remarkably constant composition and of a chemical reaction which various mechanisms serve to defend at pH 7.4.

The factors which influence reaction in blood plasma are controlled largely by renal function with the exception of the plasma content of carbonic acid which is controlled by the respiratory mechanism. The mechanism by which the plasma protein level is maintained is not known. A diagram devised by Gamble[2] illustrates the relationship of the principal components of the plasma acid-base system, together with their concentrations in plasma water (Chart 1). In listing the relative values of cations on the left and anions on the right, it is emphasized that in the body fluids we are dealing not with salts but with separate amounts of individual ions. The small amount of free carbonic acid

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on top of the diagram is not completely separated into its component ions because it is only slightly dissociated. From this chart it may be noted that sodium constitutes about 91 per cent of the base while the chloride ion is the largest component, 66 per cent, of the total acid value. The next largest item of acid structure is the concentration of bicarbonate ion (HCO_3^-), which is determined by the base in excess over the amount needed to balance the acid ions which, except for protein, are under renal control. Thus, the $B.HCO_3$ is indirectly under renal regulation; this is in distinction to the $H.HCO_3$ which is chiefly under respiratory control.

Of the various buffer systems in the blood, the free carbonic acid-base covering bicarbonate $\frac{H.HCO_3}{B.HCO_3}$ buffer is one of the most important and is fortunately easy to determine by laboratory methods. Total plasma carbon-dioxide content is a measure of carbonic acid ($H.HCO_3$), normally 3 volumes per cent or 1.35 meq. per liter plus the bicarbonate covering the base ($B.HCO_3$), normally 60 volumes per cent or 27 meq. per liter. From the normal figures for these two CO_2 components, it is evident that total CO_2 content reflects largely the $B.HCO_3$ content of the plasma.

The $H.HCO_3$ and $B.HCO_3$ are normally maintained in the blood within narrow limits in a ratio of 1:20. At this ratio, the dissociation constant is such that the plasma pH is 7.4, pH being equal to 6.1 plus $\log \frac{B.HCO_3}{H.HCO_3}$ (Henderson-Hasselbalch equation). The pH varies inversely with change in the ratio. An uncompensated increase in $B.HCO_3$, that is, an increase in $B.HCO_3$ without a relative increase in $H.HCO_3$, produces an increase in pH and an uncompensated alkalosis; an uncompensated decrease of $B.HCO_3$ produces a fall in pH, and an uncompensated acidosis. Uncompensated increase or decrease in the $H.HCO_3$ as observed secondary to derangement of the respiratory mechanism produces the opposite effect. As long as the ratio of 1:20 is maintained, changes in carbonic acid or bicarbonate do not alter the pH. Thus, there can be compensated acidosis or alkalosis with marked change in alkali reserve and little deviation of plasma pH from normal. The efficiency of the $\frac{H.HCO_3}{B.HCO_3}$ buffer system is dependent largely on the ability of the body to maintain it at a ratio of 1:20. The immediate defense of this ratio is primarily a function of the control of $H.HCO_3$ by the respiratory mechanism, and the first sign of an alteration in plasma pH is usually seen in rate and depth of respirations, since the concentration of carbonic acid in the blood is dependent upon the rate of formation of carbon dioxide in the body and of its removal from the blood by the lungs. For other anions and cations the mechanisms of absorption from the intestines and excretion by the kidneys largely determine the plasma levels. The concentration of base covering bicarbonate ($B.HCO_3$) is determined by the base which remains in excess after the union of plasma base with the anions of chloride, phosphate, sulfate, and organic acids, which are chiefly under renal control, and protein. Renal response to changes in electrolyte balance apparently is much slower in its effect than is the response of the respiratory mechanism.

For the kidneys to excrete an excessive amount of anions or cations and to re-establish acid-base equilibrium, a definitive water excretion is required and a considerable time component is involved, whereas the respiratory reaction to slight changes in plasma pH is prompt and is usually effective in preventing wide or sudden deviations from the normal. Respiratory acidosis or alkalosis develops when the respiratory mechanism to prevent plasma pH change functions inadequately.

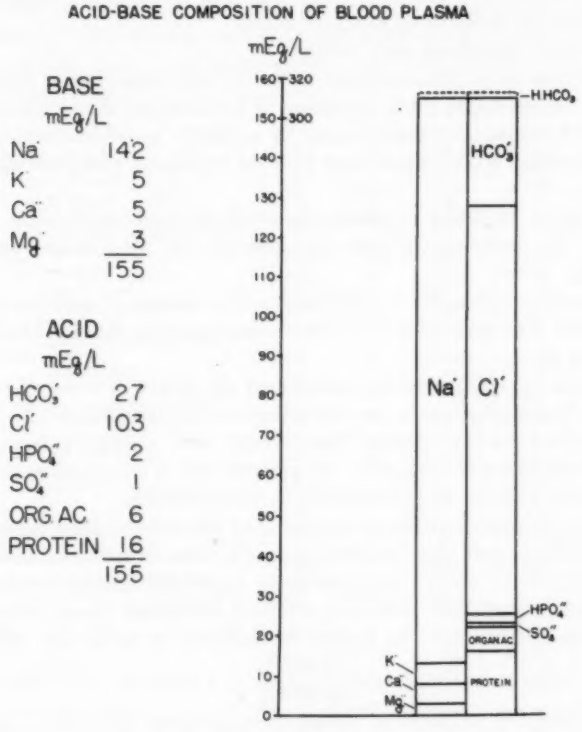

Chart 1.

CAUSES OF ACIDOSIS AND ALKALOSIS

Ordinarily, acidosis in infants and children is due to one of the following causes:

1. *Ketosis* due to accumulation of ketone bodies in the blood and tissue fluids with displacement of bicarbonate and chlorides, resulting in normal or lowered pH and lowered values of HCO_3^- and of Cl^-, with normal base. Both the lungs and the kidneys participate in the compensatory action to make room in the plasma electrolyte structure for the abnormal acid. Ketosis is seen in starvation, in diabetes mellitus, in glycogen storage disease (Von Gierke's), and in the presence of acute infection.

2. *Renal acidosis* due to failure of renal function and to the accumulation of fixed anions in the blood plasma; probably also to base loss due to failure of ammonia production and subsequent drain on plasma cations. Infants and children with dehydration and subsequent anuria temporarily presenting the picture of renal acidosis outnumber patients with permanent renal injury.

3. *Gastrointestinal acidosis* due to the loss of base as in diarrheal disease or to the ingestion of acid-producing salts such as calcium chloride, ammonium chloride, or other fixed anions. With diarrheal disease, the resulting dehydration may cause superimposed renal acidosis.

Alkalosis in childhood may follow:

1. *Vomiting of gastric contents with Cl^- loss,* depletion of the chlorides of plasma and extracellular fluid, extension of bicarbonate in the plasma to balance this loss, and consequent disturbance of carbonic acid-bicarbonate buffer system with resultant high bicarbonate content of plasma and possibly an elevated plasma pH.

2. *Excessive ingestion of alkali,* especially sodium bicarbonate, which serves to increase the bicarbonate concentration of the plasma and may result in elevated pH.

The accompanying chart lists the common causes of acidosis and alkalosis together with the customary chemical measurements usually obtained in such cases (Chart 2).

The three types of acidosis mentioned all result in lowered total bicarbonate in the blood plasma, so we have become accustomed to think of acidosis as characterized by low plasma bicarbonate, and of high plasma bicarbonate as usually indicative of alkalosis. In general this is true, and reaction of blood plasma usually follows total bicarbonate concentration.

Also, in acidosis or alkalosis, as outlined previously, the primary alteration is in the $B.HCO_3$ and the respiratory mechanism is normal; and so in metabolic acidosis there occurs compensatory hyperventilation, producing loss of $H.HCO_3$, and in metabolic alkalosis, shallow breathing which aids retention of $H.HCO_3$. In this manner, in metabolic acidosis or alkalosis, the respiratory mechanism helps to maintain the $\frac{H.HCO_3}{B.HCO_3}$ in a ratio of 1:20, thus often inducing a compensated acidosis or alkalosis with little alteration of the normal plasma pH despite marked changes in the $B.HCO_3$ or alkali reserve.

In respiratory acidosis and alkalosis with derangement of the respiratory mechanism and primary alteration of $H.HCO_3$ rather than $B.HCO_3$, prompt pulmonary defense of $\frac{H.HCO_3}{B.HCO_3}$ is impaired, compensation occurs slowly, and there may be a persistent alteration of plasma pH.

MECHANISM OF RESPIRATORY ACIDOSIS

Increased carbon-dioxide tension in the blood associated with respiratory acidosis has been observed to result from: (1) an increase of carbon dioxide in the alveolar air due to excessive carbon dioxide in the atmosphere; (2) obstruction to the escape of carbon dioxide from the alveoli, or (3) prevention

of the transport of carbon dioxide from the blood to the alveoli through the various states of asphyxia; and (4) following the suppression of respirations by effects on the central nervous system of drugs such as morphine and infections such as poliomyelitis.

Conditions interfering with the escape of carbon dioxide from the blood develop in patients with pulmonary edema (caused by toxic irritations, infections, or cardiac decompensation), pulmonary emphysema, and pulmonary fibrosis. In infancy we have observed carbon-dioxide retention in cases of emphysema due to extensive bronchiolitis, that is, a pathologic condition in which, because of inflammatory swelling and collections of thick, viscid mucus in the bronchioles, there was obstruction to the adequate escape of carbon dioxide from the lungs.

	BLOOD				URINE
	pH	CO_2	Cl	Na	REACTION
ACIDOSIS					
RESPIRATORY ACIDOSIS					
CAUSE					
1. RETENTION OF CO_2	LOW	ELEVATED	LOW	NORMAL	ACID
A. PULMONARY DISEASE		OR	OR		OR
B. HEART DISEASE		NORMAL	NORMAL		ALKALINE
C. HYPOPNEA (CENTRAL)					
METABOLIC ACIDOSIS					
CAUSES					
1. EXCESSIVE PRODUCTION OF	NORMAL	LOW	NORMAL	NORMAL	ACID
ORGANIC ACIDS	OR		OR		
A. DIABETES MELLITUS	LOW		LOW		
B. STARVATION					
C. GLYCOGEN STORAGE DISEASE					
2. ACID RETENTION	NORMAL	LOW	NORMAL	NORMAL	ACID
A. RENAL DISEASE	OR		OR		
B. DEHYDRATION	LOW		LOW		
3. INGESTION OF MINERAL ACIDS OR ACID PRODUCING SALTS i.e. $CaCl_2$ OR NH_4Cl	NORMAL	LOW	INCREASED	NORMAL	ACID
4. EXCESSIVE LOSS OF BASE	NORMAL	LOW	LOW	LOW	ACID
A. DIARRHEA	OR				
B. ADDISON'S DISEASE	LOW				
ALKALOSIS					
RESPIRATORY ALKALOSIS					
CAUSE					
1. HYPERVENTILATION	ELEVATED	LOW	NORMAL	NORMAL	ALKALINE
A. SALICYLATE INTOXICATION		OR			OR
B. MENINGITIS OR ENCEPHALITIS		NORMAL			ACID
C. HIGH ALTITUDES					
METABOLIC ALKALOSIS					
CAUSES					
1. LOSS OF HCl	NORMAL	ELEVATED	LOW	NORMAL	ALKALINE
VOMITING	OR				
	ELEVATED				
2. INGESTION OF ALKALI	NORMAL	ELEVATED	NORMAL	INCREASED	ALKALINE

Chart 2.

With obstruction to the escape of carbon dioxide from the alveoli or from other causes listed heretofore, there is an increase of carbon dioxide in the blood. Of the two forms in which carbon dioxide occurs in the blood, the $B.HCO_3$ which is dependent on residual base and renal control is the more fixed, and so the increase is relatively greater, at least at first, in the $H.HCO_3$ fraction, with a disturbance in the 1:20 ratio. As pH is equal to 6.1 plus log $\frac{B.HCO_3}{H.HCO_3}$, the increase in $H.HCO_3$ causes a reduction in pH and an uncompensated acidosis. To compensate, there needs to occur an increase in $B.HCO_3$, which could be made possible by renal reduction of chloride, permitting accumulation of $B.HCO_3$ and return of the carbon-dioxide-bicarbonate buffer

system toward the normal ratio of 1:20. In some cases return is incomplete and the plasma pH may remain low, especially if fluid intake is poor and renal excretion is impaired. It is of interest to note that if in compensated respiratory acidosis the cause of the condition leading to the increase of carbon dioxide in alveolar air should be removed suddenly, the carbon dioxide may escape rapidly, leaving an excess in the blood of uncompensated $B.HCO_3$. The patient would then quickly present a picture of alkalosis and even tetany. This train of events has been observed after tracheotomy in patients with laryngeal obstruction.

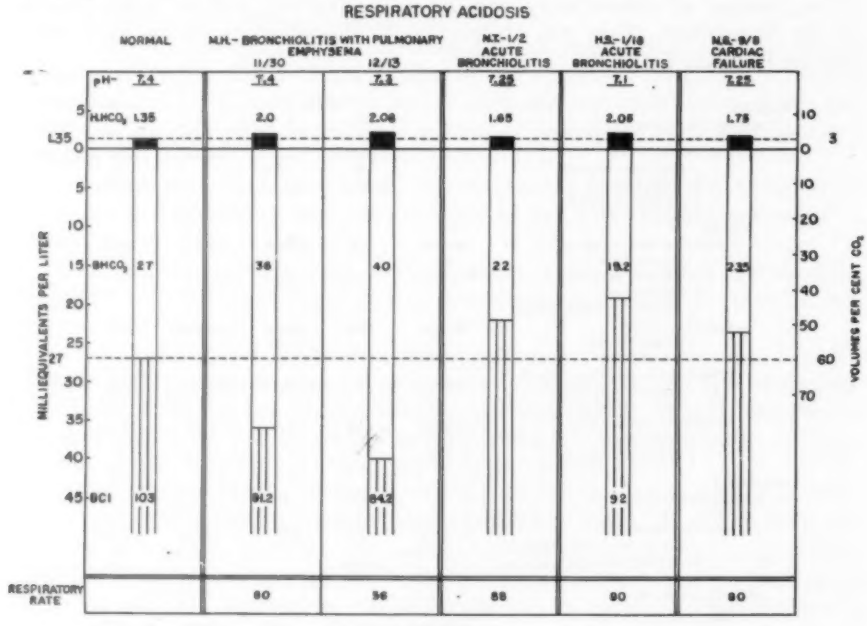

Chart 3.

The demonstration of acidosis when the respiratory mechanism is responsible requires the determination of total carbon-dioxide content of the blood plasma which measures carbon dioxide both as $H.HCO_3$ and $B.HCO_3$ and the measurement of plasma pH. The greatest change in the total carbon-dioxide content may not be in the $H.HCO_3$ but rather the $B.HCO_3$. The symptoms of acidosis in a patient with a total plasma bicarbonate as high as 88 to 99 volumes per cent become explainable when measurement of pH is made in addition to total bicarbonate determinations. Much clearer definition of the problem would be achieved with $H.HCO_3$ and $B.HCO_3$ measured separately. However, from measurement of pH and total bicarbonate the ratio of $H.HCO_3$-$B.HCO_3$ can be computed.

Two further findings in patients with respiratory acidosis merit consideration. One is the low plasma chloride noted in some of these patients. The

reduction in blood chloride is probably due to a renal compensatory adjustment to the accumulation of carbonic acid in the blood plasma; thus, when an excess of $H.HCO_3$ accumulates in the plasma, chloride excretion through the kidneys would leave more base available to permit an increase in $B.HCO_3$ and return $\frac{H.HCO_3}{B.HCO_3}$ toward the 1:20 ratio. That this is the mechanism permitting increase in $B.HCO_3$ rather than through extension of total base has been demonstrated by a number of investigators[2-4] and was observed in one of our patients (Chart 3). The urine at first should then be acid. Davies and associates[5] showed that in acute cases of respiratory acidosis there was diuresis, with doubling of ammonia excretion and increased acidity of the urine. The chloride excretion was not measured. It would seem, however, that to facilitate renal compensation of respiratory acidosis, fluids such as saline or Ringer's solution with their high chloride content are contraindicated, as they would interfere with the attempt of the kidney to lower plasma chloride and thereby permit increase of $B.HCO_3$.

The second finding that deserves explanation, especially in view of the necessity for increased chloride excretion, is the presence of alkaline urine in one of our patients, M. H. In that patient, however, the $B.HCO_3$ had increased to 80 plus volumes per cent and had largely compensated for the $H.HCO_3$ increase as evidenced by pH of 7.3. It would then seem that no longer needing to accomplish the preferential excretion of chloride, the kidneys had begun to share the respiratory responsibilities of ridding the body of excess carbon dioxide in the form of HCO_3^-. It is unfortunate that the source of the covering base was not measured. However, that the kidneys can be but slightly effective in taking over the respiratory function of removing carbon dioxide becomes apparent when it is recalled that in the adult as much as two pounds of carbon dioxide may demand excretion through the lungs in twenty-four hours.

Thus, it can be seen how misunderstanding of respiratory acidosis and alkalosis may arise when pH determinations of the plasma are not made and the condition is judged by the reaction of urine or by carbon-dioxide content of the blood plasma. The retention of carbonic acid may truly upset normal mechanisms and result in extension of carbonic acid and bicarbonate in the plasma, but with the appearance in the patient of signs of acidosis. The extension of bicarbonate occurs in order that the 1:20 ratio of the carbon-dioxide-bicarbonate buffer system may be maintained, but in many cases there is enough failure of this mechanism to permit a persistently low pH. The increase in bicarbonate covering base may not occur, and when it does not, there is less compensation and still lower plasma pH. This is illustrated in patients H. S. and N. T. in contradistinction to patient M. H. (Chart 3).

CASE REPORTS OF RESPIRATORY ACIDOSIS IN INFANCY

M. H., a 3-week-old infant, was admitted to the Babies and Childrens Hospital of Cleveland on Nov. 24, 1945, with a chief complaint of rapid labored breathing. Following birth, no respiratory embarrassment was observed for the first forty-eight hours. On the third day of life the patient's respirations became labored. The rate became rapid, and difficult expirations and expiratory wheezes were noted. Occasionally large amounts of

mucus collected in the nasopharynx. On admission, the respiratory rate was 36 per minute but later varied between 50 and 80 per minute. There was generalized cyanosis, the chest was markedly increased in anterior-posterior diameter and was hyperresonant to percussion. Supraclavicular and substernal retraction occurred during inspiration. Fine crepitant and sonorous râles were heard throughout the chest with the greatest intensity at the bases. The heart and spleen were on the right, the liver on the left.

The white blood cell count was 26,000 at the time of admission, dropping gradually in the next few days to 11,500. The red blood cells numbered 5.5 million and the hemoglobin was 61 per cent. The urine was acid in reaction. Five days after admission, on Nov. 29, 1945, the plasma pH was 7.3 with a total carbon-dioxide content of 98.9 volumes per cent. During the early hospital days the plasma pH remained at 7.3 with the total carbon-dioxide content varying between 83 and 99 volumes per cent. The plasma $H.HCO_3$, therefore, ranged between 4.2 and 5.7 volumes per cent and the carbon-dioxide tension between 66-99 mm., an increase which at its height was almost twice normal. The plasma chlorides were lowered to around 300 mg. per cent (85 meq. per liter). Roentgenograms of the chest showed an area of consolidation in the medial portion of the right apex. A shadow, thought to be caused by atelectasis, protruded from the left hilus and extended almost to the axillary line. The most striking feature, however, was the bilateral increased radiability of the peripheral lung fields.

A diagnosis of diffuse bronchiolitis with secondary emphysema was made. The clinical findings together with the elevated plasma carbon dioxide, lowered pH, and reduced chlorides led to a secondary diagnosis of partially compensated respiratory acidosis. The acute symptoms seemed unrelated to the situs inversus of the major organs. The infant was treated with steam inhalation, aspiration of the pharynx, and administration of expectorants as well as of penicillin in usual dosages. Improvement was gradual but recovery from the acute process was never complete.

In the previous patient, our first chemical studies were not done until the eighteenth day of her illness. Subsequently, we set out to determine whether, early in bronchiolitis, despite increased rate and depth of respirations, there was enough elevation of plasma $H.HCO_3$ due to decreased ventilation to make respiratory acidosis an important factor in that disease. Chemical measurement of plasma pH and total carbon-dioxide content was obtained in twenty-one infants presenting the clinical picture of bronchiolitis. In two of these patients, early in the disease, there was evidence of elevation in the plasma $H.HCO_3$ with resultant respiratory acidosis.

N. T., a 5-week-old white boy, was admitted on Jan. 2, 1947, with a history of illness of one day's duration. He was a poorly nourished infant appearing acutely and critically ill. He was comatose and exhibited an ashen gray pallor; temperature was 37.4° C., pulse 140, and respirations were 80 and shallow. The expansion of the chest was equal, percussion was resonant, but on auscultation there were many fine and coarse râles heard in both lung fields. Streaked densities in the right upper lung field and in the region of the right cardiophrenic angle were observed in the x-rays of the chest. The left lung appeared clear. The plasma pH was found to be 7.25 and the carbon-dioxide content 52.9 volumes per cent or 23.8 meq. per liter, indicating a plasma $H.HCO_3$ of 3.6 volumes per cent or 1.6 meq. per liter and carbon-dioxide tension of 55 mm. Despite the use of expectorants and chemotherapy and other efforts to relieve bronchiolar obstruction, the respirations remained rapid, between 80 and 100. On the fourth hospital day, the child suddenly had a massive hemorrhage from a duodenal ulcer which proved to be fatal. The presence of the ulcer was deemed unrelated to the acute pulmonary disease.

H. S., aged 20 months, was admitted to the hospital Jan. 19, 1947, with a history of having had frequent attacks of asthmatic bronchitis or bronchiolitis since the age of 15 months. It had been noted two days before entry that the patient was breathing rapidly.

On admission the child appeared acutely and seriously ill. The temperature was 40.4° C., pulse 140, and respirations were 88. Expiration was prolonged but there were no wheezes. There was slight cyanosis. The chest was distended and the A-P diameter seemed increased. There was slight dullness to percussion over the right lower lobe. Crepitant râles were heard in the right chest posteriorly and rhonchi were present throughout the chest. The urine was found to be acid in reaction. The white blood cell count was 17,500, of which 72 per cent were polymorphonuclear leucocytes. The plasma pH was 7.1; the total plasma carbon-dioxide content 47.5 volumes per cent or 21.3 meq. per liter, and the plasma $H.HCO_3$, determined on the basis of the foregoing, was 4.5 volumes per cent or 2.0 meq. per liter, and the carbon-dioxide tension 67 mm. The chlorides were 92 meq. per liter. Steam and hydriodic acid were instituted in an effort to relieve the bronchial obstruction and chemotherapy to combat the infection. On the second day respirations were slightly less rapid, 60 per minute, but were still labored. The urine was scant, acid in reaction, and contained 4 plus albumin. The plasma pH was 7.28; carbon-dioxide content 35.5 volumes per cent or 15.9 meq. per liter; $H.HCO_3$ 2.1 volumes per cent or 0.97 meq. per liter; carbon-dioxide tension 32 mm. and chlorides 106 meq. per liter. Despite all therapy, temperature rose to 42.5° C. that day and the child expired.

In this infant, during his first day of hospitalization, there was enough elevation of plasma $H.HCO_3$ in the presence of a relatively normal $B.HCO_3$ to produce a plasma pH of 7.1. These chemical changes plus the pulmonary findings presented the picture of an uncompensated respiratory acidosis. On the second day the situation changed. Apparently there had occurred enough decrease in the bronchial obstruction to allow the plasma $H.HCO_3$ to fall from 4.5 volumes per cent to 2.1 volumes per cent. However, during the same period the plasma CO_2 content also fell so that despite the decrease in plasma $H.HCO_3$, an uncompensated acidosis, although less severe than the first day, still persisted, with a lowering of the pH to 7.28. The oliguria and marked albuminuria suggest that the decrease in plasma carbon-dioxide content might have been secondary to renal dysfunction and that a renal acidosis had occurred terminally.

The chemical findings in these patients are pictured in Chart 3.

While cyanosis characterizes inadequate oxygen exchange in lungs, rapid labored respiration should call attention to the possibility of carbon-dioxide elevation due to limitation of ventilation capacity. Davies and co-workers[5] in cases of respiratory acidosis in adults, observed respiratory volumes as great as 30 L. per minute. In our cases, obstruction of bronchioles seemed to be the common cause of respiratory acidosis, an obstruction which usually was so far down the bronchial tree and so in the periphery of the lung fields that aspiration from above would fail to relieve the condition. Our patients have been acutely ill with fever, rapid respirations, distended, barrel-shaped, emphysematous chests, and with numerous râles throughout the lung fields. Oxygen has failed to relieve the embarrassment, although it may improve the patient's color. It has been suggested that oxygen administration, by increasing the viscosity of the bronchial secretions, may actually increase the bronchiolar obstruction.[6] Atropine and codeine on the same basis should probably be avoided. Bronchial dilator drugs as ephedrine together with the use of expectorants such as hydriodic acid and steam inhalation would appear indicated. The increased humidity has seemed to be most helpful in decreasing the

viscosity of the bronchial mucus and relieving the obstruction. Chemotherapy has been only occasionally effective. If the deep pulmonary obstruction is relieved, the acid-base relationship promptly returns to normal and the child's respirations, which have been rapid, labored, and deep and have failed to respond to oxygen inhalation, return to a normal level.

Just as instances of respiratory acidosis have been recognized, so have cases presenting the picture of respiratory alkalosis.

MECHANISM OF RESPIRATORY ALKALOSIS

The mechanism responsible for the development of respiratory alkalosis is hyperventilation with an increase in rate and depth of respiration. In patients with salicylate intoxication, with meningitis or encephalitis, or with hyperpyrexia, hyperventilation seems dependent on disturbance of the respiratory center. In a rapid ascent to high altitudes, respiratory alkalosis may result from the difference between intrapulmonary and atmospheric carbon-dioxide pressures. In both instances, hyperventilation induces loss of carbon dioxide, first from the alveoli of the lungs and then from the blood.

As in respiratory acidosis, there is a derangement of the $H.HCO_3$-$B.HCO_3$ ratio in the plasma. With loss of CO_2 from the lungs there is a diminution in the free carbonic acid of plasma which, unless compensated by a decrease of $B.HCO_3$ results in a decrease in ratio of 1:20 and an increase in pH and an uncompensated alkalosis.

To compensate for the uncontrolled loss of carbon dioxide through the lungs, there needs to be a decrease in $B.HCO_3$. This could occur through elevation of chloride ion which would decrease the residual base available for combination with HCO_3^- and, therefore, the $B.HCO_3$. That an increase in chloride ion does occur in respiratory alkalosis has been pointed out by Peters and Van Slyke,[7] Gamble,[2] and Guest and co-workers.[8] Some investigators have further noted that in patients with respiratory alkalosis there also occurs an increase in plasma lactic acid and ketone bodies by a mechanism not understood.[9] Such a change could also aid in the decrease of the $B.HCO_3$ and the return of the plasma pH toward normal.

The task of compensation, with the respiratory system deranged, rests largely on the renal mechanism. As the kidney attempts to maintain the osmotic pressure and the total base at a constant level in the blood, to lower the $B.HCO_3$ to balance the fall in $H.HCO_3$, it would have to retain chloride or other anions. This could be accomplished by preferential excretion of HCO_3^- over Cl^- with the production of an alkaline urine. Actually, as reported by Collip[10] and Davies,[5] this tends to occur to some degree after forced hyperventilation before the adjustment of chlorides gets under way. However, over a prolonged period, such a way to reduce $B.HCO_3$ might be poor physiologically because it involves a progressive loss of base. In our patients the urine continued to be acid in reaction despite plasma pH levels between 7.5 and 7.8. This may have been a factor in the maintenance of an uncompensated decrease in $H.HCO_3$ with persistently elevated pH and uncompensated alkalosis.

With the respiratory mechanism deranged and with the renal mechanism unable to cope rapidly with the situation, it would seem that the correction of respiratory alkalosis should be sought by correction of the cause of the hyperventilation. However, to help renal efforts to restore acid-base balance, the administration of chloride would appear indicated. In cases of respiratory alkalosis due to respiratory center dysfunction, administration of drugs such as morphine to inhibit the respiratory center may prove effective. It appeared to be of benefit in our first patient, B. T. In dogs, Rapaport and Guest[11] found barbiturates more effective than morphine in controlling the hyperventilation secondary to salicylate intoxication. In respiratory alkalosis due to ascent to high altitudes, pressurized breathing equipment will usually restore normal relationship.

The diagnosis of respiratory alkalosis as of respiratory acidosis is dependent on estimation of both the total plasma carbon-dioxide content and plasma pH. The chemical findings in respiratory alkalosis are those of normal or decreased carbon-dioxide content and elevated pH. This is in contrast to findings in metabolic alkalosis such as follows vomiting where there is an increase in total carbon-dioxide content and normal or elevated pH.

CASE REPORTS OF RESPIRATORY ALKALOSIS IN CHILDREN

B. T., a 9-year-old white boy, was admitted to the private service of Babies and Childrens Hospital on May 26, 1946, with a history of migratory joint pains and fever of five days' duration. On admission the temperature was 39.2° C., pulse 80, respirations 24, blood pressure 96/50. Abnormal physical findings were limited to the heart and extremities. The heart did not appear to be enlarged; sounds were of good quality and normal except for a blowing systolic murmur which was heard over the apex and was transmitted to the axilla. Pain was elicited on palpation of the left knee. There was no redness or swelling of any of the joints. Blood examination showed a red blood cell count of 4.0 million with 75 per cent hemoglobin and a white blood cell count of 7.9 thousand, of which 88 per cent were polymorphonuclear leucocytes. Sedimentation rate by the Westergren method was 72 mm. in one hour (normal under 10). The urine was normal. At 8 P.M., the day of admission, the attending physician started the patient on an infusion of 1,000 c.c. of normal saline containing 10 Gm. sodium salicylate. Six hours after the start of the infusion, the child had received 900 c.c. and approximately 9 Gm. sodium salicylate. At that time it was noted that the respirations were deep; the child was extremely restless, complained of excessive thirst, and had two episodes of emesis. The infusion was immediately stopped. Through the remainder of the night the child remained restless and disoriented and kept visualizing objects such as snakes and monkeys. The respirations remained about 28 per minute but were increased in depth. On chemical examination of the blood the next morning, the plasma pH was found to be 7.6 and the total carbon-dioxide content was 35.7 volumes per cent or 16.1 meq. per liter, indicating that the plasma $H.HCO_3$ was lowered to 1.1 volumes per cent or 0.51 meq. per liter and that the carbon-dioxide tension was 16 mm. The nonprotein nitrogen was 27.5 mg. per cent and the blood salicylate level was 810 μg per cubic centimeter. The urine showed a specific gravity of 1.006, acid reaction, and no albumin, sugar, or acetone. Intravenous administration of lactate Ringer's solution was started and attempts were made to increase the plasma $H.HCO_3$ by having the patient rebreathe his expired air and later having him breathe a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. The child resisted both procedures and during that day had several short generalized convulsions. Sodium phenobarbital, one grain intramuscularly, was also tried but had no effect on either rate or depth of respiration. At 5:30 P.M. the plasma pH was 7.6 and the carbon-dioxide content was 40.4 volumes per cent or 19.7 meq. per liter. Fluids were forced by mouth and

an infusion of 500 c.c. of 5 per cent glucose in water was started. By midnight the child had received a total of 2,640 c.c., of which 700 c.c. had been administered intravenously, and had excreted 640 c.c. of urine. The urine was consistently acid. By midnight the respirations had increased in rate to 32 per minute and were still deep. The child at that time was given morphine sulfate, ⅙ grain subcutaneously. An hour later the patient seemed much more comfortable, respirations had become slower, falling to 24 per minute, and were less deep. The child was still slightly disoriented. By noon of May 28, the child had received another 1,290 c.c. of fluid orally and had excreted 300 c.c. of urine which was again acid in reaction. Chemical measurements of the blood then showed the pH still to be 7.6, carbon-dioxide content was 56.8 volumes per cent, or 25.5 meq. per liter; chloride was 92 meq. per liter; sodium 140 meq. per liter and salicylate level was 331 μg per cubic centimeter. Sedimentation rate at this time done by the Westergren method showed a fall of 84 mm. in one hour. At 4:30 P.M. the child was much improved. The plasma pH had fallen to 7.55 and the carbon-dioxide content was 59.3 volumes per cent or 26.7 meq. per liter. The urine remained acid in reaction. On May 29, the child appeared to be well oriented, his respiratory rate was 24 per minute but breathing was still deeper than normal. The child's general reaction seemed normal except that he was drowsy. The plasma pH was 7.55 and the carbon-dioxide content was 59.6 volumes per cent or 26.9 meq. per liter. The chloride was 92 meq. per liter; sodium was 141 meq. per liter and the salicylate blood level was 140 μg cubic centimeter. Urine was acid. On May 30, respirations dropped to 20 per minute and subsequently remained normal both in depth and rate. May 31, the plasma pH had fallen to 7.46; the carbon-dioxide content was 62.5 volumes per cent or 28.1 meq. per liter. Five days later the patient was restarted on sodium salicylate, one gram by mouth every eight hours. The child remained on this dosage without any ill effects for approximately one month, during which time the sedimentation rate slowly fell to normal. On June 24, sedimentation rate was 9 mm. in one hour by the Westergren method (Chart 4).

C. N., a 7-year-old white girl, was admitted to the hospital on Nov. 15, 1946, with a history of having had some vague pains in the extremities since the preceding spring. Three days before admission she had complained of precordial pain and had been noted to have dyspnea, malaise, and fever. On admission she appeared well developed, slightly undernourished, but not acutely ill. Temperature was 37.7° C.; pulse 110; respirations 34; blood pressure 100/70. Weight was 20.9 kg. On physical examination the heart did not appear to be enlarged. Rhythm was regular but there was a moderately loud, harsh systolic murmur heard best at the apex and slightly transmitted to the axilla. The urine was normal. The red blood cell count was 4.35 million with 9.5 Gm. of hemoglobin. The white blood cell count was 7.15 thousand, of which 59 per cent were polymorphonuclear leucocytes. The sedimentation rate was 65 mm. in one hour by the Westergren method.

During the first hospital day the patient received by mouth a total of 5 Gm. of sodium salicylate. At the end of that time she vomited, complained of tinnitus, and the respirations, although remaining at the rate of 34 per minute, were increased in depth. Nov. 17, 1946, the blood pH was 7.48 and the carbon-dioxide content was 47.7 volumes per cent or 17 meq. per liter and the blood salicylate level was 400 μg per cubic centimeter. During that night the child continued to have some emesis and an infusion of 1,500 c.c. of glucose in saline was started. The morning of Nov. 18 the child appeared lethargic, the respirations had increased in rate to 48 per minute and were still labored. The child, however, remained well oriented and had no convulsive movements. At this time the pH of the plasma had risen to 7.50 and the carbon-dioxide content was 46.4 volumes per cent; the salicylate level was 260 μg per cubic centimeter. The urine was acid with a pH of 5.5. Respirations remained between 30 and 40 on November 19 and 20, but fell to 22 on November 21 (Chart 5).

A. K., an 11-year-old white girl, was admitted to the hospital on July 26, 1946, with a history of having had migratory joint pains and fever of five weeks' duration together with evidence by examination of mitral valve involvement. She had had one episode of migratory arthritis two years before admission, at which time there had been no evidence of cardiac disease. On admission the temperature was 38.1° C.; pulse 128; respirations 24; blood pressure 126/46. Weight was 37.1 kg. The child appeared apprehensive and chronically ill.

B.T. - AGE 9 YRS. (ACUTE RHEUMATIC FEVER)

	5/26	5/27 A.M.	5/27 P.M.	5/28 A.M.	5/28 P.M.	5/29	5/30	5/31
SYMPTOMS:								
HYPERPNEA	–	++++	++++	++	+	+	–	–
RATE OF RESP.	24	28	32	26-18	24	24	20	20
CONVULSIONS	–	+	+	–	–	–	–	–
DELIRIUM	–	++	+	–	–	–	–	–
TINNITUS	–			+	+	–	–	–
BLOOD:								
pH		7.6	7.6	7.6	7.55	7.55		7.47
CO_2 VOL.%		35.7	40.4	56.8	59.3	59.6		62.5
Cl m.eq/L.				92		92		
Na m.eq/L.				140		141		
URINE:								
REACTION		ACID	ACID	ACID	ACID	ACID		
ACETONE		–	–	–	–	–		
SALICYLATE:								
BLOOD LEVEL g/CC.		810		331		140		0
DOSAGE I.V.	9 GM.	–	–	–	–	–	–	–

Chart 4.

C.N. - AGE 7 YRS. (ACUTE RHEUMATIC FEVER)

	11/16	11/17	11/18	11/19	11/20	11/21
RESPIRATIONS:						
RATE	34	34	48	40-30	40-30	22
DEPTH	–	+++	+++	++	++	–
BLOOD:						
pH		7.48	7.50			
CO_2 VOL.%		37.7	46.4			
URINE:						
pH			5.5			
SALICYLATE:						
BLOOD LEVEL g/CC.		400	260			
DOSAGE (ORAL)	5 GM.	–	–	–	–	–

Chart 5.

Abnormal physical findings were limited to the heart. There was a marked increase in precordial activity. The heart was slightly enlarged to the left, rhythm was regular, sounds were of fair quality. At the apex, both sounds were replaced by a low rumbling systolic murmur and a soft blowing diastolic murmur which continued until systole. Pulmonic second sound seemed to be slightly accentuated. By x-ray the heart was enlarged; the right border of the cardiac silhouette appeared normal; the left border was unusually rounded in its upper half so that instead of presenting a concavity in the region of the pulmonary arch there was a convexity. The electrocardiogram was within normal limits. The red blood cell count was 3.62 million with 63 per cent hemoglobin. The white blood cell count was 8.6 thousand of which 68 per cent were polymorphonuclear leucocytes. The urine was normal. The nonprotein nitrogen was 22.3 mg. per cent and carbon-dioxide content was 50.3 volumes per cent or 22.6 meq. per liter. The sedimentation rate by the Westergren method showed a fall of 75 mm. in the first hour. The child was started on sodium salicylate, one gram, and sodium bicarbonate, one gram, to be given five times a day. Four days after entry, July 30, the child had some nausea and emesis and the sodium bicarbonate was discontinued. It was then first noted that the respirations were slightly more rapid than on admission and increased in depth. The rate varied between 30 and 32 per minute. On August 1 the blood salicylate level was 695 μg per cubic centimeter. On August 2 the rate and depth of respiration were further increased, the rate varying between 36 and 40. At that time chemical examination of the blood revealed the total plasma carbon-dioxide content to be 37.3 volumes per cent or 17 meq. per liter; the pH to be 7.55; the salicylate level was 545 μg per cubic centimeter. Salicylates were discontinued for a period of forty-eight hours. On August 4, the respirations had decreased in rate to 24. Salicylates were again started in a dosage of one gram four times daily and in two days the respiratory rate again showed an elevation, this time to 40 per minute with a marked increase in the depth of the excursions. On August 6 the plasma carbon-dioxide content was 32.2 volumes per cent and the pH was 7.6. The salicylate level was 276 μg per cubic centimeter. Salicylates were again discontinued and on August 7, although the respiratory rate seemed unchanged, the depth of the excursions was less marked. Total plasma carbon-dioxide content was then 55.6 volumes per cent or 25 meq. per liter; the pH had dropped to 7.4 and the blood salicylate level was 60 μg per cubic centimeter. August 8, the rate and depth of respirations had returned to normal. The total plasma carbon-dioxide content was 47.3 volumes per cent and pH 7.4. Urine during this period was consistently acid in reaction. There were no convulsions or disorientation (Chart 6).

M. A. V., a 9-year-old white girl, was admitted to the hospital Sept. 17, 1946 for treatment of acute rheumatic fever and rheumatic heart disease. During the hospital admission, while the child was receiving sodium salicylate, 0.64 Gm. every six hours, it was noted that the respiratory rate increased from a level of 20-28 to 50, and that the depth increased markedly. With the increase in rate and depth of respirations there were no untoward symptoms such as disorientation, emesis, or tinnitus. Chemical examination of the blood, however, showed a salicylate level of 308 μg per cubic centimeter; a total plasma carbon-dioxide content of 52.8 volumes per cent or 23.7 meq. per liter; and a pH of 7.62. The urine pH was 7.2. The salicylates were discontinued and it was seventy-two hours before the respirations returned to normal; subsequently, the child was restarted on sodium salicylate 0.32 Gm. four times daily. With this, there was no alteration in respirations and a check of the blood revealed the pH to be 7.49 with a total carbon-dioxide content of 59.7 volumes per cent or 26.9 meq. per liter.

The course in the foregoing patients has been described in some detail, since the wave of enthusiasm for massive salicylate therapy portends an increase in the number of cases of respiratory alkalosis that may be observed subsequent to salicylate poisoning. The mechanism whereby salicylates produce hyperventilation appears to be by direct stimulation of the respiratory center.[11] It is to be noted that in the milder cases an increase in blood pH occurred shortly

after the administration of salicylates had induced increased rate and depth of breathing. Not all patients developed tinnitus and emesis, but the more severe cases did show such symptoms and in one patient tetany and convulsions ensued. Furthermore, a considerable period was required to clear the blood of salicylates after the administration of the drug had been stopped, and until such time the respirations remained deep and the pH of the blood elevated. None of these patients with salicylate poisoning showed evidence of acidosis.

A.K. - AGE 11 YRS. (ACUTE RHEUMATIC FEVER)

	7/26	7/27 → 8/1	8/2	8/4 → 8/5	8/6	8/7	8/8
RESPIRATIONS:							
RATE	24	24-30	36	24-30	40	40	26
DEPTH	-	- +	+++	+	+++	+	-
BLOOD:							
pH			7.55		7.6	7.4	7.4
CO_2 VOL.%	50.3		37.3		32.2	55.6	47.3
URINE:							
REACTION			ACID			ACID	ACID
SALICYLATE:							
BLOOD LEVEL #/CC.			545		276	60	
DOSAGE (ORAL)	5 GM. DAILY		-	4 GM. DAILY	-	-	-

Chart 6.

The question has arisen as to why sodium bicarbonate was not administered to some of our patients in an effort to increase the salicylate excretion. Theoretical considerations lead one to presume that use of sodium bicarbonate may render more marked the alkalosis, thus increasing the tendency to tetany and convulsions, while experience in one case showed definitely that use of sodium bicarbonate in conjunction with the sodium salicylate did not prevent the appearance of respiratory alkalosis. To permit physiologic compensation to excess carbon-dioxide loss, chloride administration would appear indicated.

C. K., aged 3 years, was admitted to the hospital on Dec. 20, 1946, with signs of meningitis of probably two weeks' duration and coma and convulsions of one week's duration. Temperature was 40.5° C.; pulse 120; respirations 64 per minute.

She was a well-developed, well-nourished white girl, spastic, comatose, and breathing deeply and rapidly. Spinal fluid was under increased pressure, was turbid, and contained 13,750 polymorphonuclear leucocytes per cubic millimeter; no sugar was found and many gram-negative bacilli were seen in direct smear which proved to be type B, *H. influenza*. Chemical examination on admission showed the plasma pH to be 7.8 and the total carbon-dioxide content 51 volumes per cent or 22.7 meq. per liter, indicating a decrease in plasma $H.HCO_3$ to 1.0 volume per cent or 0.45 meq. per liter and carbon-dioxide tension of 15 mm. Urine was neutral in reaction.

Specific therapy was instituted immediately and on Dec. 31, 1946, although the child continued to be comatose, there was a decrease in temperature and a decrease in the rate and depth of respirations. The plasma pH was found to be 7.72; carbon-dioxide content 54 volumes per cent; chloride 96 meq. per liter and sodium 138 meq. per liter. On January 2, the rate of respirations had fallen to 30 per minute but the depth was still increased. Chemical examination of the blood on that date showed a fall in plasma pH to 7.65. The total plasma carbon-dioxide content was 53.3 volumes per cent or 23.9 meq. per liter. Chloride was 100 meq. per liter and sodium was 142 meq. per liter. The urine was acid in reaction. The respirations did not return to normal depth and rate and the child subsequently succumbed to the *H. influenza* infection; however, a check of the blood analysis on January 21, when respirations were relatively normal in depth, showed the plasma pH to be 7.5, the total plasma carbon-dioxide content 53 volumes per cent and plasma $H.HCO_3$ of 2 volumes per cent (Chart 7). In this patient, where there was little decrease in $B.HCO_3$ from normal, there was less compensation and a greater change in pH than was observed in our other cases of respiratory alkalosis (Charts 4 to 6).

C.K.- AGE 3 YRS. (H. INFLUENZAL MENINGITIS)

	12/30	12/31	1/1	1/2
RESPIRATIONS:				
RATE	64	60-30	52-28	40-24
DEPTH	++++	+++	+++	++
BLOOD:				
pH	7.8	7.72		7.65
CO_2 VOL.%	51	54		53.3
Cl m.eq/L.		96		100
Na m.eq/L.		138		142
URINE:				
REACTION	NEUTRAL			ACID

Chart 7.

The observations in this patient suggest that spasticity and convulsions associated with meningitis may in some instances be due to alkalosis, secondary to hyperventilation due in turn to derangement of the respiratory center.

M. V., a 4-month-old white girl, was admitted on Aug. 5, 1947, with a chief complaint of rapid, labored respirations since 6 weeks of age. The infant had been born at term by a normal spontaneous delivery with no difficulty in resuscitation. However, during the first three months of life, she had vomited one to three times a day, the vomitus containing only food of the previous meal, no bile or blood. Since the onset of rapid respirations there had been occasional cough but no fever.

She was a poorly developed, white female infant breathing rapidly (64 per minute) with an expiratory grunt and moderate retraction of the lower ribs and sternum on inspiration. The skin was ashen pale; there was no cyanosis. The chest was resonant to percussion. On auscultation many coarse and fine râles were heard throughout both lung fields, more marked at the bases. Remainder of examination was negative.

The red blood cell count was 4 million with 79 per cent hemoglobin. The white blood cell count was 4.6 thousand c.mm., of which 20 per cent were polymorphonuclear leucocytes, 12 per cent eosinophiles, 64 per cent lymphocytes, and 4 per cent monocytes. Sedimentation rate was 9 mm. in one hour. Sputum examination revealed no eosinophiles and a culture showed alpha hemolytic streptococcus and *Staphylococcus aureus*. Tuberculin 1:1,000 was negative. Absorptive studies with fat, protein, and glucose were normal. Blood Wassermann was negative. Urine was normal and acid in reaction.

X-rays of the chest showed the cardiac size and contour to be normal. There was moderate streaking along the bronchovascular markings adjacent to the heart bilaterally.

It was our impression that the infant had a chronic pneumonitis possibly secondary to aspiration of foreign material. Inhalation by nebulization every three hours of a mixture of neosynephrin and penicillin with carbogen was followed by postural drainage. Respirations remained 60 per minute, unchanged in character, and the pulmonary findings persisted. On the fifth hospital day, Aug. 11, 1947, plasma pH was 7.6 and total carbon-dioxide content was 61.8 volumes per cent indicating a decrease in plasma $H.HCO_3$ to 1.9 volumes per cent and carbon-dioxide tension to 29 mm. On August 13 the plasma pH was still 7.6 and the total carbon-dioxide content was 63 volumes per cent. Chlorides were 86 meq. per liter.

Why the chlorides were low despite absence of vomiting for over a month is not clear. Yet, that the lowering of the chlorides was not the cause of the alkalosis would seem likely when we note that the total carbon-dioxide content was relatively normal and that the greatest alteration was in the $H.HCO_3$. This last finding plus the rapid respirations would indicate a respiratory cause for the alkalosis. The child was given ammonium chloride, 0.5 Gm. every four hours. At the end of four days, despite no change in rate or character of respirations, plasma pH was 7.45, total carbon-dioxide content was 44.6 volumes per cent, and chlorides were 100.5 meq. per liter. This compensation occurred without any change in the $H.HCO_3$, which remained at 1.9 volumes per cent.

The cause for the respiratory alkalosis in this patient was possibly anoxia. As carbon dioxide is more diffusible than oxygen, the increased ventilation necessary to maintain adequate oxygenation in such a patient might be associated with increased alveolar carbon-dioxide loss. This in turn would produce a lowering of the plasma $H.HCO_3$ and a possible respiratory alkalosis. That such a course of events follows anoxia has been reported by a number of investigators.[9, 12-14] Also, in the previously mentioned observations in twenty-one infants with acute pulmonary infection with rapid and labored respirations, six showed a plasma pH between 7.5 and 7.6 with total carbon-dioxide contents which were either normal or low.

The aforementioned case further amplifies the importance of chlorides in obtaining compensation in instances of respiratory alkalosis. However, just as in the instances of respiratory alkalosis due to hyperventilation secondary to central stimulation, actual recovery is dependent on elimination of the cause of increased ventilation which in the above patients was the pulmonary infection.

Chart 8 graphically depicts the chemical findings in some of our patients with respiratory alkalosis.

SUMMARY

Respiratory acidosis and alkalosis occur probably more frequently than is generally believed and should be considered in patients presenting derangements of the respiratory mechanism. Cases illustrating the two conditions are presented.

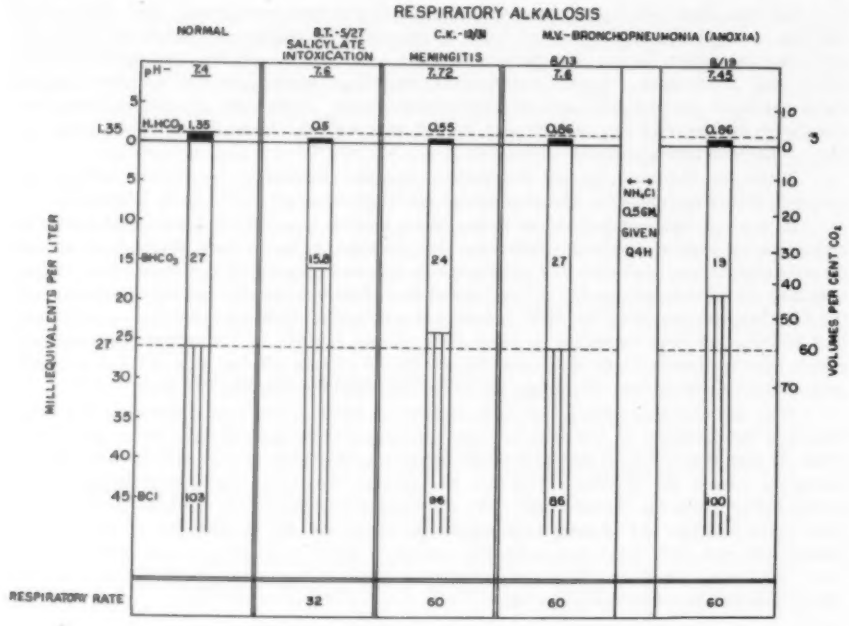

Chart 8.

TABLE I

RESPIRATORY ACIDOSIS	RESPIRATORY ALKALOSIS
1. Increased retention of carbon dioxide in alveoli produces	1. Increased escape of carbon dioxide from alveoli produces
2. Increased plasma $H.HCO_3$ which if not compensated by increase of $B.HCO_3$ produces	2. Decreased plasma $H.HCO_3$ which if not compensated by decrease of $B.HCO_3$ produces
3. Decreased pH and uncompensated acidosis.	3. Elevated pH and uncompensated alkalosis.
To compensate	*To compensate*
$B.HCO_3$ has to increase so as to return $\frac{H.HCO_3}{B.HCO_3}$ ratio toward 1:20.	$B.HCO_3$ has to decrease so as to return the $\frac{H.HCO_3}{B.HCO_3}$ ratio toward 1:20.
This can occur by:	This can occur by:
1. Increasing base available for union with HCO_3^- by	1. Decreasing base available for union with HCO_3^- by
2. Decrease of plasma chloride through	2. Increased retention of a fixed anion such as
3. Increased urinary excretion of chloride.	3. Retention of chloride by preferential urinary excretion of HCO_3^- or accumulation of other anions such as organic acids.
4. Administration of chloride appears to be contraindicated.	4. Administration of chloride appears to be indicated.

The diagnoses of respiratory acidosis and alkalosis are dependent not only on determinations of total plasma carbon-dioxide content but also of plasma pH. Whereas, in metabolic acidosis there is a correlation between the decrease in plasma carbon-dioxide content or alkali reserve and degree of acidosis, in respiratory acidosis there may be a normal or an increased plasma carbon-

dioxide content with a decrease in pH. An opposite reversal is present in respiratory alkalosis, where plasma carbon-dioxide content may be decreased or remain normal with plasma pH definitely elevated. The mechanism whereby these changes occur may be as is shown in Table I.

With the respiratory system deranged, as is the case in respiratory acidosis or alkalosis, the burden of maintaining a normal plasma pH falls more heavily on the renal mechanism. Compensation for increased or decreased $H.HCO_3$ is attempted by altering the $B.HCO_3$ so as to maintain a 1:20 ratio and thus a plasma pH of 7.4. The increase or decrease of $B.HCO_3$ seems to occur through an increase or decrease of the chloride excretion. However, compensation is usually not complete and an abnormal plasma pH persists. Efforts to increase the renal mechanism of compensation appear inadequate and it seems that the treatment of respiratory acidosis and alkalosis had best be directed toward the correction of the underlying pathology which is responsible for the derangement of the respiratory system.

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HEMATOLOGIC STUDIES ON CHILDREN OF Rh-NEGATIVE WOMEN COMPARED TO THOSE OF Rh-POSITIVE WOMEN

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THE importance of maternal immunization to the Rh factor as a cause of erythroblastosis fetalis has become well established in the last few years. The suggestion has also been made that occasional cases of erythroblastosis and a milder form of the disease called "icterus precox" may occur when the A-B blood group of the infant is incompatible with that of the mother. There are still those who also believe that physiologic jaundice is a result of A-B incompatibility of fetal and maternal blood. To date no satisfactory evidence has been forthcoming to show that Rh incompatibility between mother and infant is responsible for any disease process other than erythroblastosis fetalis but the question as to whether or not Rh or A-B incompatibility may be associated with subclinical erythroblastosis or an increased incidence of anemia or an increase in circulating immature erythrocytes has not been answered.

We have been interested, therefore, in attempting to find out whether infants whose blood is incompatible with that of the mother, either on the basis of Rh or A-B blood groups, have a hematologic pattern which differs in any way from those infants whose blood is compatible with that of their mothers. We have been concerned with the hemoglobin level, the number of erythrocytes, leucocytes, and normoblasts or erythroblasts present on the first day of life, and with the changes which take place by the end of the first week. The following studies were undertaken in the hope of determining if an infant whose blood is in any way incompatible with that of the mother can be expected to have a demonstrable anemia at the time of birth or if it can be expected to develop an anemia within the first eight days of life. We were also anxious to collect hematologic data which might serve as a standard for the infants delivered in The Chicago Lying-in Hospital.

A total of 244 infants born in this hospital between Jan. 1, 1946, and Dec. 31, 1946, were studied. No infant who weighed less than 2,500 Gm. or who had erythroblastosis or other known disease process was included. The first group was made up of the offspring of 149 Rh-negative mothers. These were taken at random but were consecutive in so far as laboratory facilities permitted. The choice was not influenced by the Rh of the father, and we were surprised to find that the numbers of Rh-negative and Rh-positive offspring were almost identical. The second group included the children of ninety-five Rh-positive mothers and was also composed of consecutive births in so far as possible. Only four infants in this group were Rh-negative.

Blood was obtained by heel puncture within the first twenty-four hours and again on the eighth day of life. Hemoglobin was determined by the Dick-

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Stevens photoelectric method, erythrocyte and leucocyte counts were made using standard pipettes, and blood smears were prepared with Wright's stain. The A-B blood types of the mothers and infants were established and all were classified as Rh positive or Rh negative on the basis of reaction to human anti-Rh_0 serum. Determinations for the presence of Rh antibodies were made on part but not all of the mothers. None were present in the bloods examined.

The results of the blood findings of the infants were first divided into groups according to the Rh type of the infant and his mother in the following manner:

Group I, mother Rh negative, infant Rh positive; 75
Group II, mother Rh negative, infant Rh negative; 74
Group III, mother Rh positive, infant Rh positive; 91
Group IV, mother Rh positive, infant Rh negative; 4

Frequency distribution charts were compiled for the data in the first three groups and the mean, median, and mode were determined for each. The mean was found the most statistically valid and was used throughout the study.

The standard deviation was determined for each mean value and the standard error between group 1 and 2, 1 and 3, and 2 and 3 was computed. Group 4 was not used because of the small number of cases it contained. In no instance was there a statistically significant difference (a figure greater than three times the standard error) between any two groups. It is thus apparent that the relation of the Rh of the infant to that of the mother had no effect on the blood picture either at the time of birth or in any change that occurred in the first eight days of life. (Table I.)

TABLE I. BLOOD FINDINGS IN RELATION TO RH OF MOTHER AND INFANT

	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Rh of mother	−	−	+	+
Rh of infant	+	−	+	−
No. of cases	75	74	91	4
Hemoglobin (Gm.)				
first day				
mean	20.7	21.0	20.6	20.1
range*	15.7 to 25.8	15.8 to 26.2	14.4 to 26.8	
eighth day				
mean	18.6	18.9	17.8	17.7
range	13.8 to 23.4	14.5 to 23.3	12.1 to 23.5	
Hemoglobin variation (first to eighth day)				
mean	−2.3	−2.4	−2.8	−2.4
range	+2.1 to −6.8	+4.0 to −8.8	+0.6 to −6.2	
Erythrocytes (in millions)				
first day				
mean	5.95	6.11	6.40	6.60
range	4.03 to 7.87	4.33 to 7.89	4.66 to 8.14	
eighth day				
mean	5.36	5.35	5.60	5.60
range	3.86 to 6.86	3.51 to 7.19	4.06 to 7.14	
Erythrocyte variation (first to eighth day)				
mean	−0.60	−0.60	−0.90	1.00
range	+.65 to −1.85	+1.11 to 2.31	+.42 to −2.22	

*Range in this and succeeding tables is given as twice the standard deviation.

Since there were no demonstrable differences between infants when the blood findings were divided according to the Rh of mother and child, all data were rearranged and divided into two groups according to A-B type. The first of these, group X, included 193 infants of homospecific pregnancies (infants whose blood did not contain an A or B isoantigen lacking in the mother) and group Y, fifty-one infants of heterospecific pregnancies (infants with an A or B isoantigen not present in the mother). Frequency distribution charts were compiled for these two groups, the means were determined, and the standard deviation for each mean value was computed. The standard error between the two groups was determined and again no statistically significant differences were found.

It is thus evident that the relation of the A-B blood groups in mother and child, like the Rh, had no effect on the blood findings at birth or in the first eight days of life. (Table II.)

TABLE II. BLOOD FINDINGS IN RELATION TO A-B GROUPS OF MOTHER AND INFANT

RELATION OF INFANT'S BLOOD TO THAT OF MOTHER	X COMPATIBLE	Y INCOMPATIBLE
No. of infants	193	51
Hemoglobin (Gm.)		
first day		
mean	20.7	20.6
range	26.3 to 15.1	25.4 to 15.7
eighth day		
mean	18.4	18.6
range	23.6 to 13.1	23.6 to 13.5
Hemoglobin variation (first to eighth day)		
mean	2.6	2.5
range	+1.8 to −7.0	+1.5 to −6.5
Erythrocytes (in millions)		
first day		
mean	6.20	6.17
range	8.02 to 4.38	7.85 to 4.49
eighth day		
mean	5.46	5.57
range	7.50 to 3.42	7.07 to 4.07
Erythrocytes (first to eighth day)		
mean	−0.80	−0.70
range	+0.54 to −2.14	+0.72 to −2.12

TABLE III. BLOOD FINDINGS IN 244 NORMAL INFANTS

	MEAN	RANGE
Hemoglobin		
first day	20.7	15.2 to 26.2
eighth or ninth day	18.4	13.5 to 23.3
Hemoglobin variation		
first to eighth day	2.6	+1.6 to −6.8
Erythrocytes (in millions)		
first day	6.19	4.33 to 8.05
eighth day	5.47	3.93 to 7.01
Erythrocyte variation		
first to eighth day	0.80	+0.58 to −2.18
Leucocytes		
first day	19,540	6,980 to 32,100
eighth day	11,560	5,840 to 17,280
Polymorphonuclear leucocytes		
first day	70.9%	53.7% to 88.1%
eighth day	49.2%	27.9% to 70.5%

Having shown, then, that Rh, A, or B antigens present in the blood of a child and absent in the blood of the mother do not influence the child's blood picture, all data were reassembled in order to determine the mean values for the entire group. (Table III.)

TABLE IV. NORMOBLASTS PER 100 LEUCOCYTES ON THE FIRST AND EIGHTH DAYS OF LIFE

Rh OF INFANT IN RELATION TO Rh OF MOTHER	INCOMPATIBLE		COMPATIBLE		TOTAL	
A-B OF INFANT IN RELATION TO A-B OF MOTHER	INCOMPATIBLE	COMPATIBLE	INCOMPATIBLE	COMPATIBLE	NO.	%
Number of normoblasts on first day of life						
0	8	51	24	88	171	70.0
1	3	4	7	19	33	13.5
2	0	4	5	11	20	8.2
3	0	1	1	5	7	2.9
4	0	0	1	2	3	1.2
5	0	2	0	0	2	0.9
6-10	1	2	1	3	7	2.9
11-20	0	0	0	1	1	0.4
Number of normoblasts on eighth day of life						
0	12	64	39	128	243	99.6
1	0	0	0	1	1	0.4
Total cases	12	64	39	129	244	100.0

TABLE V. RELATION OF A-B BLOOD GROUP TO RH OF MOTHER AND INFANT

A-B BLOOD GROUP		MOTHER Rh − INFANT Rh +	MOTHER Rh + INFANT Rh + OR MOTHER Rh − INFANT Rh − OR MOTHER Rh + INFANT Rh −	TOTAL
MOTHER	INFANT			
A	A	18	40	58
A	O	6	15	21
A	B	0	4	4
A	AB	2	6	8
B	B	6	6	12
B	O	5	5	10
B	A	0	6	6
B	AB	2	4	6
AB	AB	1	0	1
AB	A	3	5	8
AB	B	2	2	4
AB	O	0	0	0
O	O	23	56	79
O	A	4	12	16
O	B	4	7	11
O	AB	0	0	0
Total		76	168	244
Incompatible A-B		12 (15.0%)	39 (23.2%)	51 (20.9%)
Compatible A-B		64 (85.0%)	129 (76.8%)	193 (79.1%)

Examination of blood smears failed to show any difference in the number of immature blood cells in the circulation in the compatible and incompatible groups. Seventy per cent had no immature erythroblasts and over 90 per cent had two or less. In only one case were more than ten present on the first day of life and this was an infant which was compatible with its mother both in relation to Rh and A-B. One normoblast was found in the blood of one infant on the eighth day; none had been found in the smear made on the first day. In no other instances were nucleated red blood cells found on the eighth day during the course of counting 100 leucocytes. (Table IV.)

When the infants and mothers were arranged according to A-B blood groups, it was found that a somewhat greater number were incompatible on the basis of A-B blood groups among those who were compatible on the basis of Rh than among those who were incompatible. In the entire group 20.9 per cent were incompatible on an A-B basis. (Table V.)

SUMMARY

Hemoglobin estimations, erythrocyte, leucocyte, and differential counts were made on the first and eighth days of life on the blood of 244 infants. When the results were classified according to the compatibility of the A-B and Rh factors of the mother and child, no hematologic differences were demonstrable between those in which the infant's blood was compatible with that of the mother and those in which it was incompatible. Both groups were combined to give normal mean values for the first and eighth days of life.

BACTERIAL FLORA IN EYES OF NEWBORN INFANTS DURING FIRST FORTY HOURS OF LIFE

After Single Instillation of Penicillin and Silver Nitrate

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With the Technical Assistance of
Laura N. Loeb, B.S.

IN a previous communication,[1] penicillin was compared clinically with silver nitrate for prophylaxis against ophthalmia neonatorum. Penicillin was used by a multiple instillation method.

The present study was done to determine the bacterial flora of the conjunctival sac after prophylaxis, using only a single instillation of penicillin; to compare the results with those after silver nitrate prophylaxis; and to determine whether the bacterial flora of the conjunctiva was changed during the first forty hours of life.

METHODS OF PROPHYLAXIS

Prophylaxis was carried out in the delivery room within one hour after birth, and before the infant went to the nursery.

When penicillin was used, the eyelids and adjacent face area of the newborn infant were cleansed of contaminating secretions by gently wiping with a large cotton ball from the inner canthus outward. The eye was closed at the time. Gauze was then used on the fingers for traction to open the eyelids while each eye was flushed thoroughly with about 2 or 3 c.c. of sterile normal saline solution. One drop of penicillin solution was then instilled into the conjunctival sac of each eye.

Silver nitrate prophylaxis was carried out in the same manner as described above, except that sterile distilled water was used for flushing the eyes, after which one drop of silver nitrate was instilled instead of penicillin.

Penicillin was used in the form of the crystalline sodium salt of penicillin in a concentration of 2,500 units per cubic centimeter of normal saline. Silver nitrate was employed as a one per cent solution in distilled water.

PROCEDURE

The following study was done during the period in which penicillin was used as a prophylactic agent, and then repeated during the period in which silver nitrate was used. In each study, the eyes of ten infants were cultured during the interval of zero to four hours after the prophylactic treatment was given.

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Groups of ten infants were then cultured for the first forty hours at four-hour intervals. Thus, the eyes of 100 infants were cultured after each method of prophylaxis. The infants were unselected except that no infant was included whose eyes exhibited pus. Eighty-three per cent of the infants were Negro and 17 per cent white.

BACTERIOLOGIC PROCEDURES

Cultures were taken from the conjunctival sac of each eye of each infant studied. A separate sterile swab contained in a specimen tube was used for each eye, and both swabs were inserted into a sterile specimen tube containing approximately 2 c.c. of tryptose broth. The two swabs were immediately streaked across the surface of two plates containing McLeod's medium for isolation of the gonococcus, two blood agar plates, and one eosin-methylene blue agar plate. The broth in the specimen tube was then distributed in approximately equal portions into two tubes of blood tryptose broth.

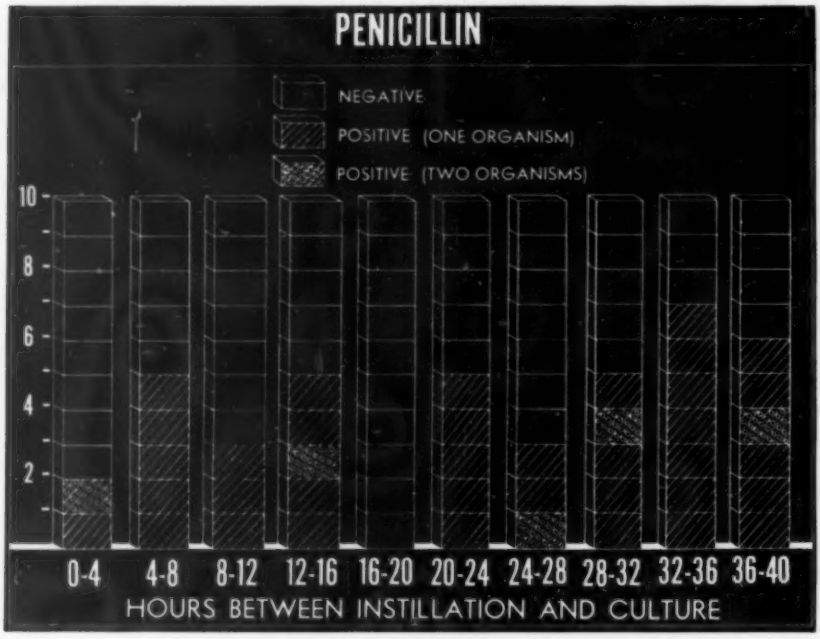

Fig. 1.—Conjunctiva cultures from 100 newborn infants at varying intervals after single instillation of penicillin. Each square represents one infant.

One tube of blood tryptose broth, one blood agar plate, and the eosin-methylene blue agar plate were incubated at 37.5° C. The other tube of blood tryptose broth and the second blood agar plate were sealed in an earthenware jar, using the Varney method for detecting anaerobic organisms, and incubated at 37.5° C. The two plates of McLeod's medium were sealed under 10 per cent carbon-dioxide tension, using the method of Wadsworth,[2] and incubated at

37.5° C. The container was a screw-top five-pound coffee jar which possessed an inner top with a rubber ring to aid in sealing.

At the end of twenty-four hours, the two blood agar plates, the eosin-methylene blue agar plate, and the two culture tubes of blood tryptose broth were examined. If negative, they were examined again at the end of forty-eight hours. At the end of forty-eight hours, the two plates of McLeod's medium were examined for colonies of Neisseriae. All plates which were negative after forty-eight hours of incubation were discarded. All broths which were negative after forty-eight hours of incubation were retained and re-examined five days after the specimen was collected. At the end of this period, if the broths were still negative, the culture was considered negative. If positive, the broths were streaked on plates and identification of the organism or organisms was made.

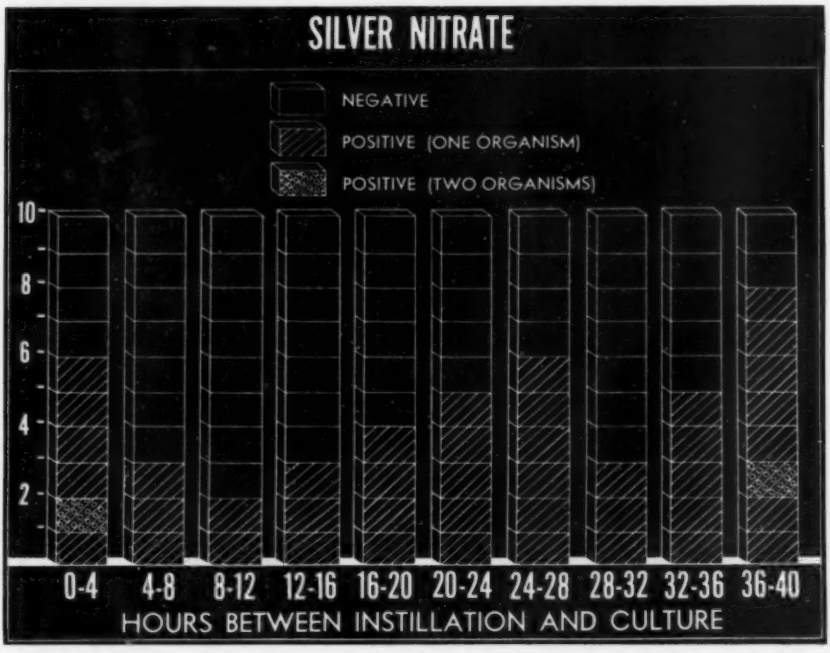

Fig. 2.—Conjunctiva cultures from 100 newborn infants at varying intervals after single instillation of silver nitrate. Each square represents one infant.

Organisms were studied as to microscopic appearance and colony formation. Staphylococci were classified as to their pigment formation, and their capacity for hemolyzing blood and coagulating plasma. The bile solubility test was used to differentiate between *Streptococcus viridans* and the pneumococcus. Gram-negative rods were grouped as to motility, pigment formation, ability to form spores, and action on carbohydrates. Gram-positive rods which gave the microscopic appearance of Corynebacteria were inoculated to carbohydrate broths to differentiate xerose, hoffmannii, and diphtheriae. All yeasts were incubated on

carbohydrate broths for identification. When colonies suggestive of Neisseriae were found on the plates containing McLeod's medium, they were tested for the "oxidase reaction." Colonies giving a positive reaction were transferred to tubes of dextrose, maltose and saccharose media which were incubated for forty-eight hours under 10 per cent carbon-dioxide tension to differentiate the varieties of Neisseriae.

TABLE I. INCIDENCE OF POSITIVE CULTURES FROM CONJUNCTIVA AFTER SINGLE INSTILLATION OF PENICILLIN AND SILVER NITRATE

PENICILLIN		SILVER NITRATE	
NUMBER OF INFANTS	POSITIVE CULTURES	NUMBER OF INFANTS	POSITIVE CULTURES
100	41	100	45

TABLE II. TYPE AND INCIDENCE IN RELATION TO TIME OF ORGANISMS FOUND IN POSITIVE CULTURES AFTER PENICILLIN PROPHYLAXIS DURING FIRST FORTY HOURS OF LIFE

ORGANISMS	HOURS BETWEEN PENICILLIN INSTILLATION AND CULTURE										TOTALS
	0-4	4-8	8-12	12-16	16-20	20-24	24-28	28-32	32-36	36-40	
Staphylococcus aureus hemolytic, plasma coagulase negative	–	1	2	–	–	1	–	1	3	–	
nonhemolytic, plasma coagulase negative	–	–	–	2	–	–	1	–	1	1	
Staphylococcus albus hemolytic, plasma coagulase negative	–	–	–	–	–	–	–	–	1	1	
hemolytic, facultative aerobe, plasma coagulase negative	–	–	–	–	–	1	–	–	–	–	
nonhemolytic, plasma coagulase negative	–	1	–	2	–	1	–	1	1	3	
Staphylococcus citreus nonhemolytic, plasma coagulase negative	–	–	–	–	–	–	–	–	1	–	26
Streptococcus beta-hemolytic, anaerobic	1	–	–	–	–	–	–	–	–	–	
nonhemolytic	–	–	–	–	–	–	–	–	–	1	
nonhemolytic, anaerobic	1	1	–	1	–	–	–	–	–	–	
nonhemolytic, facultative aerobe	–	–	–	–	–	1	–	–	–	–	6
Escherichia coli	–	–	–	–	–	–	1	2	–	–	3
Gram-positive sporulating bacillus, unclassified	–	–	–	–	–	–	1	2	–	–	3
Corynebacterium hoffmannii	1	–	–	–	–	–	1	–	–	–	2
Bacterium aerogenes	–	1	–	–	–	1	–	–	–	–	2
Pseudomonas pyocyanea	–	1	–	–	–	–	–	–	–	–	1
Diphtheroid, unclassified	–	–	1	–	–	–	–	–	–	–	1
Bacterium faecalis alcaligenes	–	–	–	1	–	–	–	–	–	–	1
Gram-negative sporulating bacillus, facultative anaerobe, unclassified	–	–	–	–	–	–	–	–	–	1	1
Totals	3	5	3	6	0	5	4	6	7	7	46

RESULTS

Positive cultures were obtained in 41 per cent of the 100 infants studied after the use of penicillin and in 45 per cent of the 100 infants studied after the use of silver nitrate (Table I).

After the use of penicillin, forty-six organisms were isolated in the forty-one positive cultures. The type and incidence of these organisms in relation to time of appearance are tabulated in Table II. After the use of silver nitrate, forty-seven organisms were isolated in the forty-five positive cultures. These organisms in relation to time are tabulated in Table III.

When the results are represented graphically in relation to time after the use of penicillin (Fig. 1), a tendency is seen for the number of positive cultures to increase. Thirty per cent of the cultures are positive during the first twenty hours of life as compared to 52 per cent during the following twenty hours.

TABLE III. TYPE AND INCIDENCE IN RELATION TO TIME OF ORGANISMS FOUND IN POSITIVE CULTURES AFTER SILVER NITRATE PROPHYLAXIS DURING FIRST FORTY HOURS OF LIFE

ORGANISMS	HOURS BETWEEN SILVER NITRATE INSTILLATION AND CULTURE										TOTALS
	0-4	4-8	8-12	12-16	16-20	20-24	24-28	28-32	32-36	36-40	
Staphylococcus aureus											
hemolytic, plasma coagulase negative	–	–	1	1	1	–	–	–	–	1	
hemolytic, plasma coagulase positive	–	–	–	–	–	–	1	–	–	–	
nonhemolytic, plasma coagulase negative	–	–	–	1	1	1	1	1	2	1	
nonhemolytic, plasma coagulase positive	–	–	–	–	–	–	–	–	–	1	
Staphylococcus albus											
hemolytic, plasma coagulase negative	1	–	–	–	–	–	–	1	–	–	
nonhemolytic, plasma coagulase negative	4	3	1	1	–	3	1	–	3	2	
nonhemolytic, plasma coagulase positive	–	–	–	–	–	–	–	–	–	1	
Staphylococcus citreus											
nonhemolytic, plasma coagulase negative	–	–	–	–	–	–	1	–	–	–	
nonhemolytic, plasma coagulase positive	–	–	–	–	–	–	–	–	–	1	37
Streptococcus											
beta-hemolytic facultative anaerobe	–	–	–	–	–	–	1	1	–	–	
beta-hemolytic, facultative aerobe	–	–	–	–	–	–	–	–	–	1	
nonhemolytic	–	–	–	–	–	–	1	–	–	–	
nonhemolytic, anaerobic	1	–	–	–	1	–	–	–	–	–	6
Bacterium aerogenes	–	–	–	–	1	–	–	–	–	–	1
Gram-negative sporulating bacillus, anaerobic unclassified	1	–	–	–	–	–	–	–	–	–	1
Gram-positive sporulating bacillus, unclassified	–	–	–	–	–	1	–	–	–	–	1
Member of Colon-aerogenes group	–	–	–	–	–	–	–	–	–	1	1
Totals	7	3	2	3	4	5	6	3	5	9	47

When the results are presented graphically after the use of silver nitrate (Fig. 2), this same tendency of positive cultures to increase with time is seen. Thirty-six per cent are positive during the first twenty hours and 54 per cent are positive during the following twenty hours.

Seven anaerobic organisms (7.5 per cent) were encountered out of a total of ninety-three. Four of these were found after penicillin prophylaxis and three after silver nitrate. Four of the seven were isolated during the first four hours, and all were isolated during the first twenty hours.

The gonococcus was not isolated from any culture.

COMMENT AND CONCLUSIONS

The bacterial flora in the eyes of 200 infants was studied during the first forty hours of life. One hundred were studied after prophylaxis employing a single instillation of penicillin, and 100 after a single instillation of silver nitrate.

The number of positive cultures was slightly less after penicillin prophylaxis (41 per cent) than after silver nitrate (45 per cent). The total number of organisms encountered in each group was approximately the same. A tendency was observed in each group for the number of positive cultures to increase with time.

That anaerobic organisms are encountered in the conjunctiva only during the first hours of life is to be expected. The oxygen tension in the conjunctival sac produces conditions unsuitable for growth.

This study indicates by bacteriologic findings that penicillin, when used as a single instillation, compares favorably with silver nitrate as a prophylactic agent, and that penicillin in this series was slightly better than silver nitrate in depressing the bacterial flora of the newborn conjunctiva during the first forty hours of life.

Further study is required for interpretation of the observed increase of the bacterial flora with time in the conjunctiva of the newborn infant.

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THE USE OF SERUM GAMMA GLOBULIN ANTIBODIES TO CONTROL CHICKEN POX IN A CONVALESCENT HOSPITAL FOR CHILDREN

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THE entrance of a person with a contagious disease into a children's hospital of a convalescent home always disorganizes the institution. A review of the patients' charts is imperative to determine those who are susceptible to the disease. The victim of the contagious disease must be transferred to his home, thus exposing others, or he must be sent to a contagious hospital. Strict quarantine must be enforced in the ward or institution in which the contagion was found, and no new admissions can be permitted until the incubation period has passed.

Chicken pox often enters institutions in spite of all preventive efforts. While it is usually not a dangerous disease, it is one of the most contagious of the exanthemata. It is difficult to isolate and may be infectious for a prolonged period. Therefore, if new admissions of unprotected children are allowed, there may be sporadic incidents for weeks.

The administration of adequate doses of pooled adult serum at the proper time to children who had definitely been exposed to measles has long been recognized as a means of modifying or preventing the development of the disease. More recently, immune serum globulin (human) has been accepted as a method for modifying or preventing measles. A test of its efficacy as a method of modifying or preventing chicken pox seemed advisable.

An opportunity to make such a test was presented when an inmate of a crippled children's convalescent hospital in Atlanta developed chicken pox. It was decided to attempt to control the spread of the disease by administering human immune globulin to all exposed children in the institution who had not had chicken pox. The child ill with the disease was transferred to the contagious hospital. Seven patients who had never had chicken pox received 2 c.c. serum globulin intramuscularly. None developed the disease, but no new admissions were permitted for eighteen days.

Seven months later, chicken pox again made its appearance in the institution. From previous experience, it seemed reasonable to keep the patient in the institution and give the serum globulin to all who might be susceptible. At the time, fifteen children had not had the disease, and these were given 2 c.c. serum globulin within twenty-four hours after the first diagnostic symptoms were recognized. Four of these came down with the disease in one, two, three, and six days, respectively, and these cases of chicken pox were not modified. As the incubation period is considered fourteen to eighteen days, these patients must have gotten the infection at about the same time and probably from the same source as the child who first showed manifestations of the disease. One very mild case developed fourteen days after the administration of the serum globulin. This could be considered one failure, even though the disease was apparently modified by the administration of the serum globulin.

A child admitted to the institution during the incubation period of chicken pox developed a case nineteen days later, though the serum globulin had been given. Another patient, to whom the serum globulin was not administered because he was said to have had chicken pox, developed the disease nineteen days later.

After several months free from contagion, a 3-year-old child was admitted to the hospital. During the night he developed a temperature of 104° F. and the following day he began to erupt with typical lesions of chicken pox. To confirm or disprove the previous experience with the administration of immune globulin (human), the patient was not sent to the contagious hospital nor isolated in any way. In the ward with this child were nine children varying in age from 3 months to 3½ years, none of whom had previously had chicken pox. Those under one year of age were given 2 c.c. of the immune globulin within twenty-four hours after the chicken pox was diagnosed; those over a year of age were given 3 c.c. None of these developed chicken pox.

The same day the case was discovered, the seven inmates of an adjoining room, varying in age from 4 to 8 years, who had not had chicken pox, were given 3 to 4 c.c. immune serum globulin, depending on age. Though these had the same night nurse, were at the same play table, and used the same bath, none contracted the disease.

In another room on the same floor the seven children of an older age group who had not had chicken pox were given 5 c.c. of the immune serum. None of these contracted the disease. All on this floor had the same nurses and used the common hallways, playgrounds, and schoolrooms.

On another floor were ten older children, eight of whom had had chicken pox. The two who had not had the disease were given 5 c.c. of the immune serum globulin. Neither of these contracted the disease.

Now no restrictions were placed on new admissions. To the six children admitted during the following nineteen days, immune serum globulin was administered, 2 to 5 c.c., depending on age. None developed the disease. After the usual incubation period of twenty-one days had passed, no new admissions were given the immunization.

Two months after this episode a 13-year-old girl who had been in the institution for a week and had a case history of having had the chicken pox developed the disease. She was not removed from the hospital or quarantined. As all the inmates had been given the immune globulin or had a history of having had the disease, none were given the immune globulin. A 14-year-old girl who said she had had chicken pox developed a typical case eighteen days later. The same procedure was followed as in the previous case, that is, no removal or isolation.

The advisability of repeating the administration of the immune globulin for fear that the passive immunity may have been exhausted was under consideration. This was answered by the entrance of a case of measles. All inmates were given the immune globulin. The case of measles was sent to the contagious hospital. No cases of measles or chicken pox developed.

Six months later a child admitted to the hospital developed chicken pox within twenty-one days. The following day, a child who had been in the institution since the previous cases of chicken pox, and who had had the immune

globulin, developed a typical case. There had been no known exposure, though a visitor might have brought in the infection or a mild case may have been overlooked. It does not seem reasonable that a carrier or delayed eruption could have survived six months. But the fact that one of the children who had been given the immune globulin now developed chicken pox when it had been protected six months seems to indicate that the immunity is exhausted in six months.

Again the same procedure was followed—no isolation or quarantine. The sixteen children who had not had the disease were given the immune globulin in the same doses as the previous cases within twenty-four hours. During the accepted incubation period of twenty-one days, sixteen admissions gave a history of not having had chicken pox. These were given the immune globulin. Eleven days after the eruption of chicken pox, ten days after the administration of the immune globulin, one child developed a mild case. The nurse counted six lesions but they were typical. There was no febrile reaction. Nineteen days after the chicken pox was noticed and eighteen days after the immune serum had been given, another child developed a typical case. This was definitely a failure. None of the children admitted during the incubation period and given the immune globulin developed the disease.

TABLE I

PATIENTS GIVEN GLOBULIN	NO. DEVELOPING CHICKEN POX AFTER EXPOSURE				UNPROTECTED	PROTECTED	% PROTECTED
	1 DAY	2 DAYS	6 DAYS	10 DAYS			
First episode 7	0	0	0	0	0	7	100
Second episode 16	1	1	1	0	2	11	85.5
Third episode 31	0	0	0	0	0	31	100
Fourth episode 23	0	0	0	1	1	21	91
Total, 77	1	1	1	1	3	70	95.8

SUMMARY AND CONCLUSION

There were four separate episodes of chicken pox in a convalescent hospital for crippled children. All unprotected children, those who had not had chicken pox, were given immune serum globulin in doses as follows:

Under one year of age, 2 c.c.
Two to 4 years of age, 3 c.c.
Four to 6 years, 4 c.c.
Over 6 years, 5 c.c.

Of the seventy-seven given the immune globulin, if the accepted incubation period is fourteen to twenty-one days, there were three failures. Seventy children were protected.

A single case of chicken pox developed, one, two, six, and ten days after the administration of the immune globulin. This experience seems to justify the conclusion that the administration of immune serum globulin (human) is of value in institutions and in selected instances when it is deemed advisable to modify or prevent chicken pox.

DOES PERTUSSIS ACTIVATE TUBERCULOSIS?

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SOME physicians contend that pertussis superimposed on active or latent tuberculosis leads to a rapid dissemination of the latter and a poor prognosis.

Many of the papers which have been written in South America, Germany, and France give the clinical impression that infectious diseases, and especially pertussis and rubella, are phthisiogenic, particularly in children. Without adequate proof and without detailed data, it has been stated that most of the fatalities in whooping cough are due to tuberculous pneumonia. Those who have said this believe that because of the enlarged thoracic glands and the continued exhausting type of cough, active or latent tuberculosis is spread through the lungs.

Some observers, Ledbetter and White,[1] and Eddy and Mitchell,[2] hold the opposite view—that is, that pertussis per se plays no active role in the activation or dissemination of tuberculosis. Morisette reported an epidemic of pertussis in a tuberculosis sanatorium for children and observed that the attack of pertussis was of short duration, of slight severity, and without sequelae, although the epidemic in the local community was unusually severe.

In a study of 2,000 cases of pertussis observed over a period of three years in Vienna, where there is a high incidence of tuberculosis, Gabriel[4] analyzed the clinical and the post-mortem findings and showed that pertussis practically never increased the activity of tuberculosis nor activated the latent form. This has also been our impression at the Cleveland City Hospital. Interest in this subject was stimulated by the following case.

N. S., a 5-year-old white girl, was admitted to the Department of Contagious Diseases, City Hospital, Cleveland, on Jan. 10, 1946. The admission diagnoses were pertussis and pneumonia. According to the history, the pneumonia occurred on Dec. 1, 1945, and the child was treated with sulfadiazine. About December 15, chickenpox developed and cleared in the usual length of time, but a coryza and purulent otitis media remained. On Jan. 1, 1946, she began to whoop. She was given rabbit antipertussis serum on January 3, but the whooping cough persisted and became worse. She was admitted to the hospital on January 10, and the diagnoses of pertussis and severe bronchopneumonia were confirmed. A cough plate was positive for *Hemophilus pertussis*, and the diagnosis of bronchopneumonia was substantiated by x-ray. A tuberculin test, 1:1,000, was negative. The patient was given additional antipertissis antiserum, but despite all therapy the course was slowly downhill and death occurred on Feb. 5, 1946. The clinical diagnoses were pertussis, bilateral bronchopneumonia, and cor pulmonale. The pathologic diagnosis was diffuse, disseminated, miliary tuberculosis.

From the Jack and Heintz Laboratory, Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University, Cleveland.

Post-mortem examination done by Dr. John Robertson revealed the body of a well-developed and well-nourished 5-year-old white girl. The heart was enlarged, weighing 125 Gm. (expected weight, 85 Gm.); the pericardium was smooth and glistening, containing 80 c.c. of straw-colored fluid with a specific gravity of 1.010; the ventricular walls were thickened, the left measuring 12.5 mm., the right 4.5 mm. The lungs were voluminous, pink, and firm without normal crepitation, and the surfaces were studded with innumerable fine nodules measuring from 2 mm. to 3 mm. in diameter, some areas being conglomerate and measuring as much as 6 mm. in diameter; all were grayish white and raised above the surrounding surfaces with no evidence of caseation or calcification. Bronchopulmonary lymph nodes near the hilum showed caseation and fibrosis, and the nodes at the tracheal bifurcation were of rubbery consistency with central caseation being present. The bronchi contained a glairy mucinous material. There was bronchogenic tuberculosis of the lungs. The bronchi and bronchopulmonary lymph nodes showed focal fibrosis and calcification consistent with the diagnosis of healed tuberculosis of the lymph nodes.

The liver, extending 4 cm. below the costal margin, was enlarged, weighing 875 Gm. (expected weight, 596 Gm.), and its surface was studded with innumerable grayish white, flat lesions measuring from 1 mm. to 2 mm. in diameter. It was sectioned with average resistance and had throughout the same grayish white nodulation as was present on the surface.

The spleen was enlarged and weighed 75 Gm. (expected weight, 47 Gm.). The capsule was smooth and glistening, but numerous grayish white, flat lesions could be seen through it.. These varied from 1 mm. to 2 mm. in diameter. On section of the spleen, the same lesions were seen throughout the splenic tissue. The remainder of the examination was essentially negative.

Microscopic examination of the liver and spleen revealed miliary tuberculosis. The bronchi and bronchopulmonary lymph nodes showed conglomerate caseous tuberculosis.

At first hand, this would seem to be an instance where pertussis contributed to or had excited tuberculosis.

Careful review of the family history and additional interviews with the family disclosed some hitherto unknown facts. The child had visited in Cleveland from May to September, 1945, in a home where there was an adult ill with active tuberculosis. Another child from a different family, exposed to the same contact, had questionable active tuberculosis. When the members of the patient's (N. S.) family moved to Cleveland in October, 1945, they resided at the house where the individual with active tuberculosis had previously lived. In addition, our patient had been in intimate contact with a child with active tuberculosis during November, 1945.

The findings were interpreted as showing organization of the mediastinal lymph nodes, placing the exposure at least as far back as November, 1945. The reaction to the tuberculin test was negative, but there probably was a slight delay in the production of the allergic phase. It is doubtful whether in this instance pertussis per se had activated or even caused dissemination of tuberculosis. It was felt that the patient would have evidenced miliary tuberculosis

and progressed as she did even if she had not had the infection of *H. pertussis*.

It could not be denied, however, that our previous conceptions were shaken, and in order to throw some light on the subject, all cases of pertussis admitted to the Contagious Hospital from 1938 to Aug. 1, 1947, were reviewed.

Since 1926, patients ill with pertussis have been routinely tested with tuberculin, since a tuberculous pulmonary infection without pertussis may simulate pertussis even to the whoop. Curiously enough, it has been shown that the evidence obtained on x-ray examination of the lungs of a patient ill with whooping cough, or measles at the height of the rash, cannot at times be differentiated from that produced by miliary tuberculosis. The reaction to the tuberculin test is, therefore, necessary information.

There were 1,747 patients admitted with pertussis. In thirty-eight patients there was some connection with tuberculosis, and these constituted the basis for the present investigation. In twenty-three, the reaction to the tuberculin test was positive, in one instance, one week after admission; in the remainder, it was negative.

In nineteen patients, a clinical diagnosis of tuberculosis, either primary or active, parenchymatous, or arrested had been made (two cases being discovered on or a few days after the patients' admission). All of these patients had a positive reaction to the tuberculin test.

The children tested were usually infants, the age range of this group (nineteen) being from 7 months to 7 years, the mean age being 13 months; 7 were whites and 12 were Negroes. Unquestionably, all but one had pertussis. The history of this one patient will be given in detail later. Three children were older and had no evidence of active tuberculosis. The twenty-third case was that of N. S., just discussed.

An analysis of the nineteen cases was made in order to show the effect, if any, of pertussis on tuberculosis.

Group I.—Nine of the nineteen patients who had pulmonary tuberculosis were found by x-ray examination to have primary active complexes without parenchymatous involvement. All nine of these patients were followed for at least one month in the hospital and for varying lengths of time after discharge. None showed any reactivation with parenchymatous spread of the primary complex. In eight of these nine patients, the primary complex showed healing even while the patient was confined to the hospital, in spite of clinically severe pertussis. The remaining patient was followed in the Outpatient Department and was completely healed in six months.

Group II.—X-ray examination of the nine remaining patients who unquestionably had pertussis showed a more diffuse tuberculous infection on admission, either tuberculous pneumonia or an infiltration too large to be considered a primary focus. Four of these patients were transferred from a sanatorium where they had been undergoing treatment for tuberculosis, and were returned to the sanatorium after recovering from pertussis. In all patients there was continued healing of the tuberculosis in spite of the pertussis; in no patient was there a delay in the healing process. It seems fair to assume that pertussis

did not cause the spread of the tuberculosis. Although this was a small series, the patients were intensively studied clinically and numerous x-ray examinations were made.

In four out of the nine cases in Group II, active pulmonary tuberculosis was diagnosed for the first time on admission. In all four of these patients, there was demonstrated acute, progressive, untreated tuberculosis. Two of the patients had been exposed to the active disease at home; one patient on admission had tuberculous cervical lymphadenitis. In all there was some spread of the tuberculous process while in the hospital. In two patients this did not occur until clinical recovery from the pertussis was apparent. All four patients were treated for tuberculosis after the attacks of pertussis.

In none of these patients was the pertussis of the severe exhausting type with prolonged weeks of coughing, which some observers state is the type which fosters tuberculosis. In three of the four patients, it was possible to deduce that the active tuberculous process preceded the infection with whooping cough. In none of the cases was the tuberculous process accelerated or very severe. All recovered completely, the tuberculosis having been apparently arrested after two years. None of the patients had miliary tuberculosis. Thus, it might be stated that the tuberculosis ran its expected course unaltered by pertussis.

The remaining nineteenth patient had tuberculosis on admission. Her history is as follows:

G. H., an 11-month-old Negro child, was admitted to the hospital on Jan. 18, 1947, because of whooping cough. Her mother insisted that she had not been exposed to whooping cough and had developed a cough with paroxysms only four days before admission. Three days before admission, she started to vomit and cough and had emesis and fever until admission. The incubation period was too short for whooping cough (one day), and a tuberculin test (1:1,000), which was negative, was done on Jan. 23, 1947. The white blood count was 26,400, 84 per cent of which were lymphocytes. The patient had a paroxysmal cough with respiratory whoop, and the lungs were filled with coarse rhonchi. The liver was slightly enlarged.

There was no history of exposure to pertussis. It was thought there was some evidence of pneumonia, and an x-ray on January 23 showed it to be present in the right upper lung. We did another tuberculin test in a dilution of 1:1,000 on Jan. 30, 1947, and this time it was positive. The histoplasmosis test was negative.

On March 9, cross-infection of measles occurred. On March 20, the x-ray showed miliary tuberculosis, and the spleen was palpable on this day. Streptomycin was started, but on Sept. 1, 1947, the x-ray showed no appreciable change. Pneumonia, as well as miliary tuberculosis, persisted in the right side of the chest, although the patient had been afebrile for seven days and had not received streptomycin for thirty days.

A second child at home, 3 years and 3 months of age, developed pertussis and was admitted to the hospital a few weeks later. This child, the mother, and the father had negative reactions to the tuberculin test, and their x-ray examinations were also negative. There was no history of exposure to tuberculosis.

All members of the family were well. The only possible predisposing factor was that the child (G. H.), when 3 weeks of age, and for three months thereafter, had lived in a crowded rooming house.

Was this patient one in whom tuberculosis was initiated by whooping cough or rubeola, or was she one who had a tuberculous infection that progressed in the usual manner? This question cannot be answered. It can be said that the child had tuberculosis before the onset of the whooping cough. Based on the fact that it takes from three to six weeks for the tuberculin reaction to become positive after infection, the child would have had the tuberculosis at least four weeks before admission, but for how much longer could not be determined, nor in this instance could one state what effect whooping cough and rubeola had on the patient's condition. She seemed to have progressed as would a patient with an ordinary infection of tuberculosis.

In the fifteen patients who had negative reactions to the tuberculin test, the diagnosis of tuberculosis was questionable and the x-ray evidence cleared as soon as did the whooping cough.

Many other patients over 5 years of age (fifty-six) who had positive tuberculin tests but no signs of pulmonary involvement, negative x-ray findings, negative family history of exposure, etc., remained well. They were not included in this report.

COMMENTS

X-ray films of the chest may show evidence of lesions which are often wrongly diagnosed as being due to tuberculosis. This is a common mistake.

In eight out of nine patients with primary active complexes there was no worsening of the active tuberculous process during or after infection with *H. pertussis*. In four patients, diagnosed for the first time on admission as having pulmonary tuberculosis, there was some spread of the disease while they were ill with pertussis. It was assumed that this was the natural course of the tuberculous infection based on the experience with this disease in a local sanatorium.

SUMMARY

There were 1,747 patients with pertussis admitted to the Cleveland City Hospital between January, 1938, and Aug. 1, 1947. In thirty-eight patients, an x-ray diagnosis of a suspicious tuberculous lesion was made. Twenty-three had positive reactions to the tuberculin test; three of the latter were in older children with negative x-ray findings, while nineteen actually had tuberculosis (excluding the patient, N. S., on whom an autopsy was performed). In no instance, save in the case of G. H., reported in detail, could any evidence be found on which to base the conclusion that the tuberculosis was activated by the pertussis. It cannot be said that pertussis does not possibly activate this disease, but all evidence is to the contrary, and the burden of proof rests on the shoulders of whoever makes this assertion. Certainly it is clear that reactivation of tuberculosis following pertussis is so rare that it is probably a coincidence.

CONCLUSIONS

Every patient ill with whooping cough, especially Negro children, should have a tuberculin test at the onset of the pertussis.

Every patient ill with whooping cough who coughs longer than a month should have another tuberculin test, for if he does not have bronchiectasis, he may have tuberculosis.

In the presence of acute whooping cough or measles, an x-ray diagnosis of miliary tuberculosis can never be made if the reaction to the tuberculin test is not known.

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FOOD ALLERGY

IV. The Function and Clinical Application of the Rotary Diversified Diet

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IT HAS been said, "from time immemorial the diet has been the cure of almost every illness, yet it has seldom proved successful in the treatment of any disease or syndrome." This statement is not a condemnation of the possible effectiveness of diet as a means of therapy, but it does emphasize two important facts. First, the constantly recurring implication that diet may be an etiologic factor in various syndromes indicates there have been many observations pointing to this probability. Second, it suggests that the clinical application of dietary manipulation may not have been carried out in a correct manner.

In this presentation I wish to discuss the function and the use of the rotary diversified diet as a therapeutic measure in allergic syndromes, to delineate the indications for its use, and to point out the pitfalls which might make its application ineffective.

I. THE NATURE OF THE ROTARY DIVERSIFIED DIET

In the case of allergy, diet may be used either as a diagnostic or as a therapeutic procedure. Rowe's[6] elimination diets are the most common ones used for the diagnosis. Gay[1] has advocated a diagnostic diet which was based on our principle of performing individual food tests, that is, a diet in which all foods are used but once in five days. Little can be found in the literature concerning diet as a therapeutic measure in the field of allergy.[2, 4] Such references do not give any details which would enable the reader to apply the dietetic procedures with accuracy. One can hardly apply the term "therapeutic diet" to the blanket indictment of "nuts," "fish," or "candies," as is often routinely done when advising patients concerning choice of foods in the case of asthma or hay fever.

I gave some of the details of this diet at the Allergy Forum in Cleveland, in 1940, and excerpts were published in *Science News* at that time. I also detailed this procedure at the St. Paul meeting of the American College of Physicians in 1941.

The diet, as reported herewith, was first employed in 1934. At that time the purpose of rotating and diversifying foods was not based upon the present concept of its functions, namely, to maintain tolerance or to prevent sensitizations from developing. It was prescribed with the idea of avoiding cumulative reactions. It was soon learned that cumulative reactions were not nearly so important as these two other factors. It became apparent that what, in most instances, was previously thought of as a cumulative reaction, was in reality, a recurrence of sensitizations.

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With the development of this diet the next logical step was to employ it to *prevent the occurrence* of new sensitizations. The method was first used in 1935 for a patient who was subject to migraine of an extreme form. This patient reported, on history taking, that she had not been free of headache a single day during the past ten years. This history was confirmed during the first several months of study. The patient would show a few days' improvement whenever placed on a compatible diet as determined by individual food tests. Then, within a matter of five to ten days, her symptoms would return to their previous intensity. She was then given a general diet, except for three foods. Every food used was rotated and diversified so that each food was repeated at a specified interval. Various types of foods were used to secure the basic dietary requirements. The details of this case and the end results have been fully covered in another paper.[5] Since that time (1935), the method has been studied in a large series of patients. Dr. Carroll Pounders began using this procedure in June, 1936 as a means of avoiding the development of new food allergies in his pediatric cases. It has also been used by Drs. Zeller, Leney, McNeill, Jackson, and Stoesser. Its value, in their hands, warrants the exposition of this method for general usage.

II. SELECTION OF FOODS FOR ROTARY AND DIVERSIFIED DIET

In selecting foods to be used for this diet, only those for which the patient has a tolerance are to be included. There will be many times when the status of tolerance cannot be ascertained accurately. However, one will do the best possible in the early stages of care, if *every food known* to be a cause of symptoms is omitted. There are certain general rules concerning food allergies that will be of value in selecting foods. It has been found that if a patient is sensitive to wheat, it is very easy to become sensitive to other members of the cereal family. If one is sensitive to one of the ripe legumes, it is often true that all members will cause symptoms; therefore these are best omitted until checked.

It has been found important to limit the use of certain foods at all times. Thus, if one can take buckwheat it is generally used at intervals, because past experience has indicated that most people become allergic to buckwheat if it is used regularly. If one is sensitive to wheat, then oats, rice, and corn are used at intervals until tests indicate other usage is feasible. It is very likely that corn will cause symptoms if it is used constantly by a wheat-sensitive person. There are, of course, exceptions to this rule.

If one is to select foods for which the patient has a tolerance, it is imperative that one has a command of the nature and changes which are characteristic of food allergy. Many of the failures in using dietary regimes are due to the fact that the user is not as well informed on the basic nature of food sensitizations as he is on the details of the diet he is using. Tolerance is, at all times, a relative thing; it merely implies that the patient has *no demonstrable symptoms, under the conditions* existing at the time of the specific test.

The frequency of use of selected foods will vary according to the conditions existing in each case. The factors to be considered are: (1) whether the food has ever been a cause of symptoms; (2) if the patient has a high or

low inherent tolerance to foods in general. Each of these two points will be considered more fully under the discussion concerning the use of the diet.

The number of feedings per day is *extremely important.* It is one normal serving at any selected meal. Thus, the rotary-diversified diet may be summarized as: a diet consisting of foods for which the patient *has a tolerance,* which will include *various types* of food necessary for a well-balanced diet. These foods are used at *intervals of two to seven days,* taking one normal serving per day at *one meal only.* Finally, it is used either to preserve tolerance, which has been acquired by omission of this food, or it may be used to prevent the initial development of food allergies, in known allergic individuals.

The use of the diet is to be guided by two cardinal facts:

1. *Its use to maintain tolerance.* This will include foods which previously have been proved to be a cause of specific symptoms but which can be used at present because tolerance has been gained by omission of the food.

2. *Its use to prevent the development of new allergies.* This will be the case, for the most part, in young patients. It is also used for adults, particularly those with low inherent tolerance.

III. USE OF THE DIET TO PRESERVE TOLERANCE

In adults this will be the most common cause for employing this procedure, although there will be a certain number of instances when it is used to avoid developing sensitizations.

Whenever a patient is proved sensitive to a food, it is omitted until tolerance develops, which is the case in the majority of sensitizations. This is a matter of three to eighteen months, varying with the patient and the syndrome. The food is checked for the first time at six months, then retested at nine months, if symptoms followed the first test. Another test is made at the end of the year; if there is still a reaction, the final test is made at eighteen months. If this test is followed by symptoms, it is best to consider the food as a permanent or fixed food allergy and discard it. At whatever test time the food fails to produce symptoms, the rotary principle of use is then applied. For six feedings it is used once daily, at five-day intervals. This is done so that if sensitization recurs, it will not mask itself. If no symptoms are induced by these six feedings, the patient is instructed to change the interval from five to three days. The food is used at this interval for three months. If still tolerated, the period may be reduced to once in two days.

There are very few foods which have been allergens that can be used after tolerance is achieved by elimination, at intervals of less than once in three days. There are such instances, however, and one may occasionally be able to reinstate a food to once daily, every day, without recurrence of active allergy. It is important to know that when a food is used once in seventy-two hours, the patient may become sensitive to it again and develop a complete masking of this allergy. Such recurrences of sensitization are insidious and progressive, as a rule. Therefore, in the course of using the diet, if the patient has an increase of symptoms, consider and evaluate the probability of the allergy recurring. If this be true, elimination must be used again, and when the food is compatible the next time the interval of usage must be doubled,

at least. Thus, if one becomes sensitive to wheat after using it three weeks at three-day intervals on the first trial, the second time it is used the interval should be six days. It is usually necessary to make a reduction of at least 50 per cent in the incidence of use, to be effective.

In the fourteen years since food sensitization was based on *demonstrable effect,* instead of upon a skin test reaction, I have not found any food which, after tolerance had been obtained, could be replaced in the diet and used with the same frequency as before the sensitization was proved, without the allergy recurring. Thus one might say, once allergic to wheat, always allergic to wheat, if the incidence of use is the same. There may be exceptions to this, *but it has not been proved,* whereas, the statement just made has been proved many times. It has been observed in patients with eczema that a food causing eczema in the baby does not necessarily cause asthma in childhood when the patient has become asthmatic. But, when a given food causes asthma at one time for this patient. it will do so as a rule, as long as the incidence returns to the old frequency. In using feedings of this type, I have been able to control symptoms of known allergens for eleven years. Then, during war-time restrictions the patient broke interval usage for two weeks and developed an active sensitization which has not subsided with six months' elimination.

If recurrence of sensitization is suspected, eliminate and re-test the food in the regular manner.

IV. USE OF THE DIET TO PREVENT THE DEVELOPMENT OF ALLERGIES

In this case the purpose in using the diet is to forestall the occurrence of an allergy. It will be used in two groups of patients, (1) the pediatric group and (2) adults. There are only superficial differences in these two groups, but with the adults many factors must be considered other than the diet, hence both usages will be delineated. Whenever a physician encounters allergy in an infant or a very young person, particularly if there are multiple allergies, it is wise to teach the patient to use this diet *as a prophylactic measure.* Since the interval use of various foods may be confusing to the mother or patient, I have devised a diet chart which makes it very easy for the cook, patient or mother, to determine the allowed foods for a given day or for days in advance. These diets are to be posted in the kitchen for ready reference.

As an illustration of the need and function of the rotary diversified diet, let us say that a one-year-old baby developed a rash which is proved to be due to oranges. Sneezing is produced by egg, and diarrhea by cod liver oil. Instead of substituting *one* fruit for the orange, have the patient use pineapple juice, *once daily, every third day.* Use prune juice in the same manner, and tomato or apple juice for the day following. Then it will be time to use the pineapple juice again. Thus, sources of vitamin "C" are diversified and rotated according to definite intervals. The patient is not sensitive to any of these rotated foods, nor is there any indication that he is about to become sensitive to them. The dietary procedure is carried out wholly to prevent the *probable occurrence of allergies,* since experience with other cases at this age indicate it is the rule, not the exception, for these patients to develop new allergies.

When new foods are added to the diet with time, these, too, may be rotated and the patient thus follows an eating pattern which gives him the advantage of using many foods, at the same time lessening to a very great degree the probability of developing sensitizations to them.

Pounders,[3] who has used this diet since 1936, states that in his present pediatric practice there are not nearly as many allergies per patient in the present 10-to-12-year-old group dieted by this method as compared with the same age group whose allergies were treated by strict elimination and nonrotating substitution of one food for another.

It should be borne in mind that if a patient has become sensitive to a common food, say wheat, and one substitutes corn for wheat, it is entirely likely that the patient will also develop an allergy to corn. In fact, it is so true that I have emphasized that the physician's first duty to a wheat-sensitive patient is to determine the status of corn as regards tolerance or sensitization. A diet based on this principle has certain distinct advantages. It has a definite purpose: it is neither distasteful nor monotonous, nor short of necessary ingredients. In comparison to diets based on eating fancies and routine, it has much to offer the allergic patient.

The second group of patients in which this diet may be used are those in whom there are a number of definitely established allergies which have existed over a period of time. For the most part, these will be teen-age children and adults. The need for the use of this type of therapeutic measure will be governed by the patient's inherent tolerance to food. This is an inherent ability which varies with the patient, and determines the ratio between the incidence of a food in the diet and the development of an allergic status.

Thus, one patient may be able to eat a given food three times daily for five years, before it becomes a cause of allergy. Another person, whose apparent degree of sensitization and severity of symptoms are identical, may develop an allergy to any food which is used three times daily for ten days, or even less. Just what this factor is, has not been evaluated at present. Nonetheless, it is of extreme importance from the clinical standpoint. It means that certain patients can be treated by a narrowing, limited diet. In these patients it is satisfactory to eliminate the known allergens, paying little attention to what substitutions are used. One may safely use a very limited diagnostic diet for these patients, for they have a factor which I have called a *high inherent tolerance* for foods (narrow base of sensitization).

In contradistinction to this type of case there are the patients whose diet cannot be restricted to a few foods, in whom elimination diets for diagnosis are not effective and often increase symptoms after being used a few days or a week. They are, as a rule, patients whose symptoms have shown little improvement by customary plans of treatment; they are pale and often have moderate anemia without an abnormal blood cell picture. This group of patients I have labelled as having a *low inherent tolerance* for foods. They tend to become sensitive to any food which appears in their diet daily. In one such case, studied in 1934, only five foods did not produce a definite increase of

asthmatic symptoms. When the patient was placed upon this diet, improvement occurred on the fifth day, but by the eighth day symptoms were as severe as before. Re-tests of these five foods produced definite symptoms following ingestion of each. The patient was then gradually placed upon a rotary diet. Foods were added when elimination had produced tolerance, until finally the patient was eating all foods at intervals of two days and most of them were used at three-day intervals. When the diet was started, the patient required between eleven to thirteen injections of epinephrine daily. After the diet was fully established, and without any other changes in inhalant therapy or living conditions, only six injections of epinephrine were needed in forty-four consecutive months, four of these on one day. The patient then confessed to the use of pork two or three times daily, for the week preceding the use of these doses of epinephrine. Pork produced symptoms on deliberate, individual food testing.

It is not suggested here that every patient with severe symptoms has such reactions from food allergy. Experience will indicate to the careful observer in which patients diet is a probable factor, and then no changes should be made in the diet until the inhalants are treated and brought under control, or the diet should apply on a prophylactic basis until such studies are complete. Then individual food testing and continuance of the diet should proceed as indicated. It must be emphasized again that one never knows the effect of foods until they are properly tested. The statement from the patient that he knows certain foods are *not a cause of symptoms, is valueless.*

Again, one should keep in mind that this is not a diagnostic diet, since foods used at intervals of three days or less can mask themselves. However, if one feeds all foods at intervals of five days or more, masking will not occur. The purpose of this diet is not to diagnose, but to preserve tolerance and to prevent the development of sensitizations. Diagnosis will be more efficient if carried out by means of individual food testing.

The use of the rotary diversified diet can best be exemplified by case reports. It should be borne in mind that the diet is used for several reasons. First, it is employed to prevent the development of new sensitizations in patients with a low inherent tolerance or a broad base of sensitization. These patients are invariably difficult ones to handle and it is imperative that one should avoid producing new sensitizations to be added to the old ones. Second, the diet is used to preserve tolerance which has been acquired by prolonged and complete omission of a known allergic food. Finally, it is of most value as a prophylactic measure in allergic children. Each of these uses are illustrated from actual case records herewith.

CASE 1.—F. H., aged 35, was seen because of constant headaches of the so-called migraine type. In the course of making the diagnostic survey on foods, it was found, after seven months' trial, that it was impossible to keep this patient on any elimination diet and free her of symptoms. This was due to the fact that additions to the diet would provoke symptoms by the time that these foods were used long enough to establish freedom of symptoms, with the elimination of her active prediet sensitizations. Accordingly, it was decided to employ the rotary diversified diet as a means of preventing these rapidly developing allergies. The procedure was as follows: Each food was tested individually, and

if it provoked neither headache nor fatigue, it was added to the diet to be used once daily every other or every third day, the interval chosen being determined by the frequency of use previous to testing. Foods taken at least daily were continued once daily every other day. Foods taken at intervals of three days or longer were used not to exceed once in three days. One food, wheat, was eaten once daily without difficulty.

There were a number of foods, specifically milk, beef, and corn, which could not be taken in any amounts at any time without producing symptoms, and they were eliminated.

The effect of the diet was not fully established for a period of several months; a point which emphasizes the time requirements for establishing diagnosis and, in turn, relief, in the allergic patient.

In this particular individual there were no breakdowns in tolerance for foods used at intervals as indicated. This should be looked upon as an unusual feature rather than the expected course in this type of patient. It is very frequently the case that sensitizations will develop when foods are shifted from once weekly or a ten-day interval to once every three days.

CASE 2.—E. P. H., aged 35, came because of chronic nasal symptoms of itching, watering, sneezing, and congestion. These were practically constant for the previous ten years. In the course of diagnosis and treatment, it became necessary to eliminate one food after another due to constantly recurring symptoms which were due to foods which had been placed in the diet and used constantly upon the elimination of a previously existing sensitization. This method of treatment was carried out until the patient was restricted to five foods which of necessity had to be used at least once daily and for the most part, thrice daily.

At that time it was my opinion that the recurrence of symptoms after assigning a food to this patient's diet for three or four days' use was evidence of a cumulative type of sensitization. Accordingly, in order to avoid cumulative reactions, these foods were added and, if they did not provoke symptoms, were repeated at intervals of once in three days. This period was chosen because it had been observed so frequently that reactions continued after individual tests for fifty-four to seventy-two hours. It was assumed that the interval chosen would avoid a cumulative reaction. Actually, it was learned in the course of time that this procedure avoided the re-creation of old sensitizations; in other words, it preserved tolerance.

With this concept in mind, a systematic program was begun which consisted of testing foods which at one time had been eliminated because they produced symptoms. These foods were admitted to the diet and used once daily at five-day intervals for six times, after which, if no ill effects were observed, the interval was changed to once daily every third day. Over a period of approximately nine months' time, it was possible to re-enter all foods save three at intervals of forty-eight or seventy-two hours. Two foods, wheat and corn, could not be used in this manner. Corn was not usable at all except in the green form (not a rare fact); wheat had to be eliminated strictly for four years and then could only be used once in five days without postingestive symptoms.

It may be questioned if a rotation of foods with single usage in the day is not a problem of considerable magnitude in the average home. The writer, having used such a procedure for years, is of the opinion that it is no more difficult than any other diet when it has been used long enough to become established. Furthermore, there is no monotony such as occurs in many present-day diets.

This diet can be followed easily by the use of the chart (see Chart I). For example: beef is assigned to Monday and Thursday, chicken on Sunday and Wednesday, lamb on Tuesday, salmon on Friday, and pork on Saturday. Orange juice, instead of being a monotonous dietary habit to start each breakfast, becomes a refreshing introduction to breakfast on Sunday and Wednesday, while

prune juice is used on Monday and Thursday, pineapple juice on Tuesday and Friday, and apple, tomato, or grape juice for Saturday. Other fruits are used in the course of each day, assuring the patient at least two good servings of fruit daily. This diet has produced eminently successful clinical results in a period of many years' time for this patient, and has been the only means of control which has proved practical, and after once being established, was self-managed, requiring only occasional suggestions and guidance.

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY

FOODS	INTERVAL USE OF FOOD	DAYS OF MONTH ON WHICH FOODS ARE TO BE TAKEN																												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Chart 1. Chart for Rotary Diversified Diet.

CASE 3.—B. S., aged 6, was seen because of eczema of several years' duration. She had been treated previously, and in the course of allergic management, had been placed upon a so-called diagnostic diet consisting of six foods. She had grown worse upon this diet and sought assistance because of the presumably incurable allergic problem.

It was discovered that three of these six foods were actually the cause of symptoms, and upon their elimination, clinical cure was effected.

In the course of discussing her problem, that is, eczema and the subsequent clinical course of the average allergic child, the mother expressed concern over what she might do to prevent the occurrence of asthma in the distant future and a recurrence of eczema in the near future. It was explained to her how to avoid certain inhalants such as excessive house dust, and how to avoid feathers, orris root, and massive pollen doses.

In the handling of the diet, the mother was advised to practice a rotation and diversification of the diet, *not because her daughter was sensitive to these foods, but to avoid sensitization, since it had already been established that the child became allergic with great ease.*

Subsequent observation has established the fact that eight years later this child is not restricted on a single food and has remained free of all allergic manifestations since following this diet.

It may well be argued that it is futile to practice means of avoiding the development of asthma in an eczematous individual. Occasional success with such patients could easily be the result of factors other than adherence to the diet. However, our experience and that of pediatricians who have used this procedure for over ten years has led to the observation that the incidence of food allergy in groups of children on whom rotation and diversification were practiced is but a small fraction of the incidence in a similar age and economic group where such measures were not used. Our combined experience is sufficient to state without equivocation that the method is of distinct value when correctly carried out.

SUMMARY

The nature, use, and indications of the rotary-diversified diet have been made. The nature of the diet is to use *one normal serving* of various selected foods, once daily, at intervals of two to seven days.

The diet is to consist of foods for which the patient has a tolerance, that is, foods which are not capable of provoking allergic symptoms.

The diet may be used to maintain tolerance for foods which have previously caused symptoms, but have become compatible by avoidance for a period of time.

The diet may also be used prophylactically to prevent the development of new allergies. This is of especial value for infants and young children but may be used at all ages.

The indications for its use are rapidly developing allergies when substitutions are made, and low inherent tolerance to foods. The diet should not be used as a substitute for diagnosis.

Since foods used at intervals, as suggested in this diet, may develop an insidious recurrence of sensitization and mask themselves perfectly, this possibility must be evaluated when suspected.

Finally, there is only one method to ascertain the effect of a food, *individual deliberate* test. When the diet is apparently failing to produce the desired results, testing is indicated.

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PHYSICAL GROWTH OF CHINESE INFANTS

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DURING the years 1935 to 1940, the writer accumulated physical growth data on "well-nourished" Chinese babies extending over the first postnatal year. It is the purpose of this paper to communicate the results from analysis of these data.

SOURCE AND SELECTION OF SAMPLE

The data were collected at three institutions, each maintaining a maternity nursery and a well-baby clinic: Margaret Williamson's Hospital in Shanghai (1935); West China Associated University Hospital in Chengtu (1937); and St. Elizabeth Hospital in Shanghai (1940-41).

Not all available infants were included in the study. The writer subjected each available infant to a medical examination and estimated its general nutritional status. A four-category classification was used: ++++ ("clinically healthy"), +++, ++, and + ("malnourished"). Infants falling in the last two categories were rejected. The subjects on which the study is based were selected accordingly. They were rated either as "clinically healthy" (++++) or only "moderately flabby" (+++).

MEASUREMENTS TAKEN

Records were obtained for body weight, stem (vertex-rump) length, and total (vertex-heels) length. Weight was taken nude, on a balance accurate to within 10 Gm. The length measurements were likewise determined with the babies lying nude. The instrument employed was a sliding calipers (a long ruler with two transverse bars, one fixed to the end of the ruler and the other movable). The procedure in measuring total length was as follows: The baby was laid with its long axis paralleling that of the ruler; an assistant held both its feet with one hand, pressed upon both knees with the other, and checked that the heels were brought into contact with the fixed bar; the writer held the infant's head by its jaw and moved the sliding bar of the instrument into contact with the vertex. The procedure in determining stem length was the same, except that the assistant elevated the infant's thighs and pressed the buttocks into contact with the fixed bar of the instrument.

FINDINGS AT BIRTH

The body size of "well-nourished" Chinese infants at birth was studied, utilizing data collected at St. Elizabeth Hospital. Table I presents the major results from analysis of these data. Weight was taken shortly after birth and the other measurements within the first twenty-four postnatal hours. For each measurement the means are slightly larger on the male infants than on the female infants. Fifty per cent of the male infants had birth weights between

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2.84 kg. and 3.25 kg.: the central one-half of the female birth weights fell between 2.82 kg. and 3.24 kg. Average stem length (vertex-rump) in this sample of Chinese neonates will be seen to approximate 68 per cent of average stature (vertex-heels).

TABLE I. THE BODY SIZE OF NUTRITIONALLY SELECTED CHINESE INFANTS STUDIED IN SHANGHAI (1940-1941)

	N	MEAN	MINIMUM	PERCENTILES 25	50	75	MAXIMUM
Males							
Weight (kg.)	118	3.23	2.5	2.84	3.08	3.25	4.0
Vertex-heels (cm.)	116	49.3	43	48.2	49.2	50.2	53
Vertex-rump (cm.)	118	33.6	28	32.7	33.5	34.3	37
Females							
Weight (kg.)	110	3.18	2.5	2.82	3.03	3.24	3.8
Vertex-heels (cm.)	114	49.0	43	48.0	48.8	49.9	53
Vertex-rump (cm.)	112	33.0	28	32.4	33.2	34.0	36

GROWTH IN WEIGHT DURING FIRST POSTNATAL WEEK

The trend of the weight curve in Chinese infants over the first week of postnatal life was studied on material collected at the St. Elizabeth Hospital. Use was made of approximately 100 subjects of each sex. Mean weight was computed on the full samples at birth and on decreasing portions of each sample at successive days following birth. Table II displays the findings. It will be seen that for both sexes there is a loss in mean weight over the first two postnatal days. The loss approximates 200 Gm., or 6 per cent, on the male infants and 170 Gm., or 5 per cent, on female infants. Between two and seven postnatal days there is registered a slight over-all trend of increase in weight.

TABLE II. MEAN WEIGHT (KG.) OF NUTRITIONALLY SELECTED CHINESE INFANTS AT SUCCESSIVE DAYS DURING THE FIRST POSTNATAL WEEK

AGE (DAYS)	MALES N	MALES MEAN	FEMALES MEAN	FEMALES N
Birth	102	3.23	96	3.18
1	74	3.12	71	3.07
2	70	3.03	66	3.01
3	52	3.08	69	3.01
4	73	3.10	64	3.04
5	71	3.09	61	3.04
6	58	3.10	50	3.05
7	35	3.07	29	3.10

GROWTH IN WEIGHT, STATURE, AND STEM LENGTH FROM 2 TO 50 WEEKS OF AGE.

In studying the physical growth of Chinese infants between the first and twelfth postnatal month, records were combined from St. Elizabeth Hospital, West China Associated University Hospital, and Margaret Williamson's Hospital. It will be recalled that one of these hospitals is located in Chengtu and the other two in Shanghai.

The records were separated for analysis by sex, measurement, and month of age. This resulted in 72 subgroups, twelve age subdivisions for each of the three measurements on each sex. Table III lists the central tendency value

(mean) of every subgroup. Inspection of Table III shows that in general Chinese male children exceed Chinese female children throughout the first postnatal year in average weight, stature, and stem length.

TABLE III. THE BODY SIZE OF NUTRITIONALLY SELECTED CHINESE INFANTS STUDIED IN SHANGHAI AND CHENGTU (1935-1941)

AGE (MO.)	NO. INFANTS	WEIGHT MEAN (KG.)	VERTEX-HEELS MEAN (CM.)	VERTEX-RUMP MEAN (CM.)
		Males		
0.5	77	3.75	52.6	35.3
1.5	202	4.76	55.7	37.5
2.5	182	5.60	58.4	39.3
3.5	141	6.26	60.5	40.7
4.5	111	6.74	62.5	41.6
5.5	95	7.16	63.9	42.5
6.5	93	7.61	65.4	43.0
7.5	79	7.94	66.9	44.2
8.5	78	8.37	68.0	44.8
9.5	66	8.38	68.7	45.1
10.5	42	8.82	71.8	46.7
11.5	46	8.85	71.9	46.5
		Females		
0.5	56	3.54	51.8	34.7
1.5	151	4.47	54.6	36.6
2.5	105	5.22	57.3	38.2
3.5	90	5.89	59.8	39.4
4.5	46	6.48	61.6	40.8
5.5	51	7.20	63.7	42.4
6.5	41	7.20	64.7	42.8
7.5	40	7.47	65.9	43.2
8.5	30	7.68	67.2	44.4
9.5	26	7.79	68.2	44.5
10.5	20	8.67	70.9	46.3
11.5	18	8.82	72.3	46.8

TABLE IV

AGE PERIOD (MO.)	WEIGHT (KG.)		VERTEX-HEELS (CM.)		VERTEX-RUMP (CM.)	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
0.5-3.5	2.51	2.35	7.9	8.0	5.4	4.7
3.5-6.5	1.35	1.31	4.9	4.9	2.3	3.4
6.5-9.5	0.77	0.59	3.3	3.5	2.1	1.7

Changes in the rate of growth of Chinese infants during the first year may be conveniently indicated by calculating the differences between equally spaced means. Differences between means from Table III representing ages three months apart are reproduced in Table IV.

For each of the three measurements there is registered a declining rate of growth with age. Note that the increase in the mean from 0.5 to 3.5 months is greater than that from 6.5 to 9.5 months by approximately 1.75 kg. for weight, 4.5 cm. for stature, and 3.1 cm. for stem length.

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SUBLUXATION OF THE HEAD OF THE RADIUS "NURSEMAID'S ELBOW"

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REPORTS of subluxation of the head of the radius, commonly called "nursemaid's elbow," are ubiquitous in the literature. Mention of it has been found as far back as in the writings of Hippocrates, but it was first accurately described by Fournier[1] in 1671. During the nineteenth century it was a favorite subject among the French and German writers. Though Gardner[2] wrote of it in 1837, Poinsot[3] in 1885, Moore[4] and Cushing[5] in 1886, and Van Santvoordt[6] in 1887, the "granddaddy" of the American articles was by Van Arsdale[7] in 1889, when he reported 100 cases and presented a thorough discussion. Since that time there have been sporadic accounts of the subject, nearly all of which have been in foreign literature. The latest article in American literature was by Anderson[8] in 1942.

The purpose of this paper is not to report an unusual occurrence, but rather to emphasize the frequency with which subluxation of the head of the radius occurs and to stress the fact that, although it is a situation involving bone and joints, it is a pediatric problem and should be treated by the pediatrist.

The word "luxation" means dislocation; subluxation, therefore, refers to partial or incomplete dislocation. Subluxation of the head of the radius is limited to children, and usually very young children, when they are most likely to be still under the care of a child specialist. The youngest reported case was a 3-month-old infant and the oldest was a 9-year-old child. By referral and conversation it has been learned that orthopedists generally are not familiar with subluxation of the head of the radius and, therefore, incur much unnecessary expense and trouble in its diagnosis and treatment. However, the subject is slighted by pediatric textbooks and only scattered few orthopedic texts briefly mention it.

The condition has been given a variety of names, including Gromyer's injury, dislocation of the head of the radius by elongation, dislocation of the head of the radius downward, and, our own favorite, nursemaid's elbow. The manner in which the injury is sustained is almost identical in every instance; that is, a sudden pull on the extended arm of a small child. Picking up a child by one arm after a fall, pulling a child from under a table, helping a child across the street and up the curb, or when one child pulls a toy from another child are all common examples of a quick pulling motion on the outstretched arm. Occasionally the condition is sustained in a fall, in which case the history may be misleading.

A typical case history is as follows:

W. J., a 3-year-old boy, was being led by the hand from one room to another by his nursemaid when he stumbled. In an effort to prevent him from falling the nursemaid quickly

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jerked his hand upward. The boy immediately cried out in pain and, upon being released, sat on the floor and refused to use the arm. He continued to cry and resisted any effort at assistance. When the pediatrician (who was called) arrived, the child was found still sitting on the floor with his left arm hanging by his side, the elbow slightly flexed so that the forearm and hand rested on his lap; the hand was in the position of pronation. The child was too tearful to be of much assistance, but it was determined that the main point of pain was at the wrist, which he fondled gently with his right hand. On examination, however, there was no limitation of motion at the wrist joint and no tenderness. On further examination it was found that there *was* tenderness over the head of the radius and, although flexion and extension of the elbow joint was accomplished, there was encountered definite resistance on attempting to supinate the hand, the effort being accompanied by a scream of pain from the child. The diagnosis of subluxation of the head of the radius was made by the physician and reduction was effected, attended by the characteristic click.

This case illustrates several important points. (1) The history of the manner in which the injury was sustained is most important and leads one to think immediately of subluxation of the head of the radius. If history is unobtainable, as is often the case when children are hurt at play, it is wise to rule out fractures and dislocations first in order to avoid doing further injury. (2) The position of the arm is characteristic. It hangs limply by the side with the elbow flexed at about 20 degrees and the hand in pronation. (3) Pain may be limited to the elbow, but more frequently it is referred to the wrist. The reason for this has never been explained adequately; some writers state that it is due to the stretching of a nerve, others say it is due to the pinching of a nerve, though how either can occur with the injury we cannot discern. (4) There is a point of acute tenderness over the head of the radius. (5) All motions of the arm and hand can be carried out with the exception of supination. Attempts at supination meet with an abrupt obstruction about midway and the child experiences severe pain. (6) No deformity can be demonstrated externally and the x-ray reveals no abnormality. Stone[9] states that if roentgenograms of both elbows are made there can be measured a greater distance from the head of the radius to the capitulum of the humerus on the affected side than on the unaffected side. Others refute this claim and roentgenologists agree that the difference is so slight that unless the condition was looked for specifically it would not, in all probability, be discovered. (7) The click heard or felt when reduction is accomplished is disputed by no one. This click in itself is assurance that the diagnosis was correct and that the treatment has been successful. Without it one cannot be sure of reduction. However, if manipulation is not followed by a click the arm may be placed in a sling and autocorrection will occur in one to two days. To illustrate this point we cite the following case.

A. S., a 4-year-old boy, was being led by the hand across a busy street by his mother and assistance was given the child in mounting the curb by lifting on the arm. The child immediately cried out with pain and refused to use the arm. A physician's office was located in the block and the child was taken there. Examination failed to enlighten the physician and the child was sent to the office of an orthopedist, who took an x-ray of the affected arm. The x-ray was interpreted as being negative. On being unable to arrive at a definite diagnosis, the orthopedist placed the child's arm in a sling and asked that he return for further examination in two days. On returning the arm was being used normally and the mother stated that she noticed it normal just that morning when the child awoke, it having been carried in the sling entirely the previous day.

Undoubtedly this was an instance of subluxation of the head of the radius. Immediate reduction was not accomplished, but when the arm was placed in a sling autoreduction occurred and the child had no further trouble.

Protean theories have been propounded to explain the pathology of subluxation of the head of the radius, but as these cases are never fatal, autopsy findings are lacking. Slight anterior or posterior displacement of the head of the radius, the locking of the tuberosity of the radius below the edge of the ulna, and the interposition of soft parts between the two bones have all been suggested and disproved. The most likely theory and the one with the most support was set forth by Stone[9] in 1916 following a number of experiments on twelve arms from the anatomy laboratory. He showed that with hyperextension and pronation the annular ligament of the elbow joint was allowed to slip over the head of the radius into the space between the head of the radius and the capitulum of the humerus. Prior to the age of 7 years the head of the radius and the shaft of the radius are of practically the same diameter,[10] allowing easy passage for the head of the radius through the annular ligament without laceration. If laceration of the ligament occurred there would be edema and induration of the joint for several days, which is not the case. Also, it is between the ages of 2 and 5 that the child is walking around with frequent lifts by the hand from taller individuals, thus making the highest incidence of subluxation at this age.

The incidence of occurrence was stated by Van Arsdale to be one per cent of surgical cases in children under 9 years of age. No other report of a sufficiently large number of cases has been made to change this figure.

Recurrences are not uncommon, especially in those children of frail stature and poor musculature.

There are no sequelae incident to its occurrence or correction.

The proper manipulation for correction and reduction of the subluxation is simple. The elbow is flexed to about 90 degrees and one thumb of the operator is placed over the head of the radius, exerting moderate pressure upon it. The patient's hand and forearm is then forcibly supinated beyond the point of obstruction. If the operation has been successful the characteristic click can be heard or felt and the child will begin to use the arm. If the subluxation has been standing overnight there will be some edema of the elbow joint and the child will not use the arm immediately in spite of reduction. It is best to place the arm at rest in a sling for a day or two in cases of this sort.

SUMMARY

The subject of subluxation of the head of the radius has been presented again to stress the frequency with which it occurs and to bring out the fact that, because of its limitation to small children, it is a pediatric problem and should be treated by the pediatrician. The diagnosis is made on (1) the suggestion of the history, (2) the lack of deformity at the site of injury, (3) point tenderness over the head of the radius, and (4) the loss of function and the typical position of the extremity. Treatment consists of moderate pressure over the

head of the radius with forceful supination of the hand. Successful treatment is accompanied by the characteristic click.

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BLOOD CHEMICAL AND IMMUNOLOGIC EFFECTS OF ADRENAL CORTICAL EXTRACT IN CHILDREN

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IN EXPERIMENTAL animals, a single injection of pituitary adrenotrophic hormone or adrenal cortical extract causes a decrease in total leucocyte count, a decrease in the absolute number of lymphocytes, an increase in the absolute number of polymorphonuclear leucocytes, and an initial increase in hemoglobin and erythrocyte count.[1, 2] These changes are evident three hours after the injection. They are maximum nine hours after the injection in the case of pituitary adrenotrophic hormone and six hours after the injection in the case of adrenal cortical extract. Adrenalectomy, on the other hand, causes a trend toward anemia, absolute lymphocytosis, and decreased polymorphonuclear leucocyte production.[2]

Lymphocytes of normal rabbits have been shown to contain a protein fraction identical with the gamma globulin of the serum.[3] It has also been recently demonstrated that antibodies are concentrated in lymphocytes.[4, 5] Marked anamnestic response of agglutinin titers to washed sheep erythrocytes has been demonstrated to be produced by injection of adrenal cortical extract or adrenotrophic hormone in mice previously immunized to washed sheep erythrocytes following the lapse of a sufficient interval of time to allow these titers to fall to zero.[6] A similar phenomenon was demonstrated in rabbits.[7] Coincident with this and with the development of lymphopenia there has also been demonstrated a small but significant increase in serum proteins.[8] This increase is in the globulin fraction.[3]

Injection of adrenal cortical extract causes hypercholesterolemia in rabbits.[9]

In adrenalectomized animals, none of these changes occur following the injection of pituitary adrenotrophic hormone, but they do occur following the injection of adrenal cortical extract.

It was felt that it would be interesting to determine if doses of adrenal cortical extract of reasonable size for clinical use would produce similar effects in human subjects.

MATERIALS AND METHODS

The studies reported were carried out on six children, 3 to 14 years of age, four of whom were hospitalized for fractures and two for physiotherapy treatment for postpoliomyelitis paralysis. These patients were all bedridden throughout the experiment. None of them showed any evidence of glandular disturbance or malfunction of any type.

Each child was given an injection of 1 c.c. of pertussis vaccine (40,000 million per cubic centimeter)* on each of two occasions, two weeks and one week before the beginning of the experiment.

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*Produced by Cutter Laboratories, Berkeley, Calif.

On the days of the experiment the children were allowed the regular hospital dinner at 11:30 A.M., blood samples were drawn at 3 P.M., a standard meal consisting of five soda crackers and a pint of milk was given at 5:30 P.M., and blood samples were drawn again at 9 P.M. On the first experimental day subjects 1, 3, and 5 were given an injection of 5 c.c. of adrenal cortical extract† immediately following the withdrawal of the first blood sample at 3 P.M. Subjects 2, 4, and 6 were used as controls. One week later the experiment was repeated with subjects 1, 3, and 5 being used as controls and subjects 2, 4, and 6 being used as experimental subjects, each receiving an injection of 8½ c.c. of adrenal cortical extract immediately after the withdrawal of the 3 P.M. blood sample. Thus, blood samples were drawn from the experimental subjects immediately before the injection of adrenal cortical extract and six hours after its injection, and blood samples were drawn from the control subjects at corresponding times. In this way each subject was used once as an experimental subject and once as a control subject. The data could thus be paired in such a way that each subject served as a control for himself as an experimental subject.

On each of the blood specimens drawn the following determinations were done: hemoglobin, erythrocyte count, leucocyte count and differential, sedimentation rate (read at 20, 40, 60, and 80 minutes), blood glucose, serum cholesterol, total and fractional protein, and pertussis titer. On each day a Tiselius electrophoretic pattern was obtained on the pooled serum of the three experimental subjects both before the injection of adrenal cortical extract and six hours after its injection. All hematologic determinations were carried out by the same graduate technician using the standard methods routinely employed by the University of Minnesota Hospitals. Pertussis titers were done by Dr. A. C. Kimball of the Minnesota Department of Health. Electrophoretic analyses were done by Dr. D. R. Briggs of the Division of Agricultural Biochemistry of the University of Minnesota. Blood chemistry determinations were done by one of us (V. C. K.) by standard micro methods.

For the electrophoretic studies, exactly 2 c.c. of serum from each of three subjects was pooled to give a total sample of 6 c.c. This pooled sample was dialyzed for three days at a temperature of 4° C. against a sodium veronal buffer of pH 8.6 and ionic strength of 0.1, the buffer being changed each day and the final dialysis being made against a volume of 3 L. of buffer. The serum specimen was then clarified by centrifugation and diluted to a total volume of 25 c.c. with the buffer against which the final dialysis had been made. This buffer was also used to fill the electrode chambers of the electrophoresis cell. The electrophoretic patterns of these diluted sera were then obtained after 7,500 seconds of electrophoresis under a potential gradient of 7.03 volts per centimeter by the "schlieren scanning" method of Longsworth.[10]

Blood pressure, pulse, respirations, and temperature were recorded at hourly intervals throughout the experiment.

RESULTS

The results of the cholesterol and sugar determinations are shown in Table I. The data are paired such that the values obtained for each subject on the

†Produced by the Upjohn Company, Kalamazoo, Mich.

day he was used as a control and on the day he was used as an experimental subject are shown side by side. As will be noted from the table, the cholesterol level at 9 P.M. was lower than that at 3 P.M. in all cases in which no adrenal cortical extract was injected and higher in all cases in which adrenal cortical extract was injected. Thus the injection of adrenal cortical extract apparently caused an increase of the cholesterol level in all cases. Analysis of the data on the sugar determinations in the same manner reveals that the effect of injection of adrenal cortical extract was a decrease in the blood sugar concentration in five of the six cases.

Similar analysis of the data on hemoglobin, erythrocyte counts, leucocyte counts, differential counts, sedimentation rates, total protein, albumin, and albumin-globulin ratios revealed no consistent changes in either direction.

TABLE I. EFFECT OF INJECTION OF ADRENAL CORTICAL EXTRACT ON CHOLESTEROL AND GLUCOSE LEVELS

SUBJECT NO.	TIME (P.M.)	GLUCOSE (MG. %)		CHOLESTEROL (MG. %)	
		CONTROL*	EXPERIMENTAL*	CONTROL*	EXPERIMENTAL*
1	3	131	109	165	140
	9	106	78	155	155
	Difference	−25	−31	−10	+15
2	3	91	109	245	190
	9	93	93	220	190
	Difference	+2	−16	−25	0
3	3	96	80	87	110
	9	80	73	78	118
	Difference	−16	−7	−9	+8
4	3	72	105	197	155
	9	83	87	183	167
	Difference	+11	−18	−16	+12
5	3	83	107	218	172
	9	93	90	208	195
	Difference	+10	−17	−10	+23
6	3	65	91	165	172
	9	80	80	144	184
	Difference	+15	−11	−21	+12

*Figures in the columns designated "experimental" represent levels of glucose and cholesterol determined on blood drawn just before and six hours after the injection of adrenal cortical extract. In the column designated "control" are the levels determined on blood drawn at corresponding times of the day, but on these days no adrenal cortical extract was injected.

TABLE II. EFFECT OF INJECTION OF ADRENAL CORTICAL EXTRACT ON PERTUSSIS TITERS

SUBJECT NO.	TIME (P.M.)	CONTROL DAYS*	EXPERIMENTAL DAYS*
1	3	1-320	1-640
	9	1-640	1-640
2	3	1-640	1-1280
	9	1-640	1-1280
3	3	Neg.	Neg.
	9	Neg.	Neg.
4	3	1-1280	1-640
	9	1-640	1-320
5	3	Neg. (±1-20)	Neg.
	9	Neg. (±1-80)	Neg.
6	3	1-160	1-80
	9	1-160	1-80

*Figures in the column designated "experimental day" represent titers of blood drawn just before and six hours after the injection of adrenal cortical extract. In the column designated "control day" are the titers of blood specimens drawn at corresponding times but on these days no adrenal cortical extract was injected.

In Table II are presented the pertussis titers. It will be noted that there are no significant effects on these titers following the injection of adrenal cortical extract.

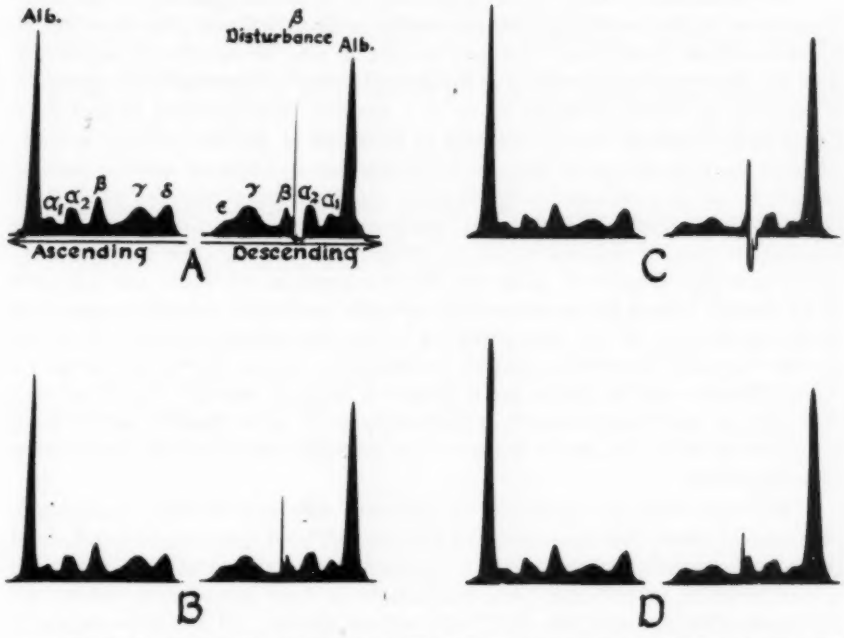

Fig. 1.—Electrophoretic patterns of pooled serum specimens drawn before and after the administration of adrenal cortical extract.
A, pattern of pooled serum of subjects 1, 3, and 5 before administration of adrenal cortical extract.
B, pattern of pooled serum of subjects 1, 3, and 5 six hours after administration of adrenal cortical extract.
C, pattern of pooled serum of subjects 2, 4, and 6 before administration of adrenal cortical extract.
D, pattern of pooled serum of subjects 2, 4, and 6 six hours after administration of adrenal cortical extract.

The electrophoretic patterns obtained from the pooled specimens of serum are shown in Fig. 1. It will be noted that the ascending patterns of corresponding serum specimens are virtually identical. Calculations of the proportions of the various electrophoretic components present did not reveal any significant differences between the samples drawn before the injection of adrenal cortical extract and those drawn six hours after its injection. However, in the case of the descending patterns there is an interesting difference in appearance between the patterns of sera drawn before the injection and six hours after the injection of adrenal cortical extract. In the former, the beta disturbance peak is located on the side of the beta-globulin peak toward the alpha globulin peak and in the latter on the side toward the gamma globulin peak.

There were no significant changes noted in blood pressure, respirations, pulse, or temperature during the course of these experiments.

DISCUSSION

The significance of the observation of a shift in the position of the beta-disturbance in the descending electrophoretic patterns following the injection of adrenal cortical extract is not apparent, but it may be mentioned in passing that we have previously noted the beta-disturbance in electrophoretic patterns of the sera of normal children to be in a position corresponding to that here found in the samples drawn previous to injection of adrenal cortical extract, whereas the type of curve obtained following the injection of adrenal cortical extract is the one commonly observed in electrophoretic patterns of sera of adults. There is evidence[11] that the beta disturbance is associated with a weak lipoprotein complex existing in the components of the beta globulins which becomes partially dissociated when the beta components are under the influence of an electric field in the absence of the albumin and alpha-globulin components of the serum (i.e., in the descending leg of the electrophoretic cell). It would appear that this lipoprotein complex is altered in such a way as to change its electrophoretic mobility under the influence of injected adrenal cortical extract. However, an exact interpretation of this phenomenon is not justified until a more conclusive proof of the precise nature of the normally occurring beta disturbance is forthcoming.

We have found no significant or consistent difference between hemoglobin, erythrocyte count, leucocyte count or differential, total lymphocyte count, total polymorphonuclear leucocyte count, sedimentation rate, total and fractional serum proteins, or pertussis titer determinations done immediately before and six hours after the injection of adrenal cortical extract. It has been suggested by Dougherty,[12] in agreement with our own conclusions, that the discrepancies between these findings and those previously reported on experimental animals might be explained on the basis of the fact that the doses of adrenal cortical extract injected in this experiment were considerably smaller in relation to the weight of the subjects than were the doses in the animal experiments. The doses used in this experiment were chosen because it was desired to determine the effects of clinically feasible amounts of material for injection. It would be desirable to repeat this study using amounts of adrenal cortical extract comparable, in terms of cubic centimeter per unit of the subject's body weight, to the amounts used in previous animal experiments. Such a study is contemplated.

SUMMARY

The data presented confirm in human subjects the finding of elevated cholesterol levels following the injection of adrenal cortical extract. They further suggest a tendency toward a lowering of the blood sugar level following the injection of this material.

A shift in the position of the beta disturbance in the descending electrophoretic patterns was observed in these same subjects.

A complete hemogram, sedimentation rate, total and fractional serum protein, and pertussis titer studies failed to show any significant changes.

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CONGENITAL HEMOLYTIC ICTERUS, FOUR GENERATIONS

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IN THE clinical study and treatment of two cases of familial hemolytic anemia or acholuric jaundice, a careful study of the histories, particularly the maternal histories, in four generations, was made, confirming the hereditary factor of the condition.

Campbell and Warner,[1] in their careful analyses of this subject, emphasized that the disease is inherited as a Mendelian characteristic, though there are no data to indicate the result to be anticipated from parental stigmata of the condition on both sides, as such a coincidence has not been reported, but this hereditary characteristic is transmitted to 50 per cent of the offspring of the first generation with subsequent hereditary dominant and recessive radicals.

The disease presents many varying degrees of clinical manifestations and as Weber[2] has demonstrated, the forms of the disease may be characterized by jaundice, anemia with no apparent jaundice (though adequate tests may show an increase in the serum bilirubin), splenomegaly, or the asymptomatic members of the family may only show increased fragility of the red blood cells.

Typically, a case of the disease would show a hypochromic, microcytic type of anemia, with reticulocytosis, increased red blood cell fragility, and with jaundice, splenomegaly, and fever. The finding of any one of these in a member of a family where the disease has been diagnosed marks this individual with a subclinical type of the disease.

The disease may first manifest itself in infancy or childhood, as in the congenital type, or in adults, in the latent type, and is frequently aggravated by acute illness.

CASE REPORTS

CASE 1.—B. S., an 8-year-old white girl of English-American parentage, in good nutritional status, was acutely ill with a chief complaint of nausea, vomiting, malaise, fever (104° F.) and yellowish skin. The maternal grandmother and a maternal aunt have histories of familial hemolytic anemia. There are two brothers, one living and well, and two sisters, one living and well. An aunt (maternal) had a splenectomy. Past history was negative. The patient first became ill on March 19, 1946, when she complained of anorexia, nausea, vomiting, and headache. She had a fever and a yellow tinge to the skin which grew progressively more pronounced. The mother noticed the yellowish tinge to skin and the similarity to the condition seen in the grandmother and aunt. Physical examination revealed a pale, thin child with a yellow tinge to the conjunctiva, a spleen palpably enlarged to within four fingerbreadths of the midline, three below the costal margin, and tender to pressure; all else was apparently normal.

Listed below are dates of transfusions, hemograms, and data obtained from laboratory reports:

March 22, 1946.—Hemoglobin was 40 per cent, red blood cells, 2,100,000; white blood cells, 6,100; polymorphonuclears 66 per cent, lymphocytes 31 per cent, monocytes 2 per cent and eosinophiles 1 per cent. Marked anisocytosis and moderate eccentric achromia were present, with many microcytes and few poikilocytes, and a few cells showing slight polychromatophilia. There was no basophilic stippling or nucleated red blood cells. There was a marked degree of anemia, of combined type, with definite leucopenia and relative increase in lymphocytes. The icterus index was 20. The Van den Bergh direct reaction was negative, indirect was 3.7 mg. per 100 c.c.

On March 23, 250 c.c. citrated blood were given. Hemoglobin was 21 per cent, red blood cells 1,320,000, white blood cells 4,800, polymorphonuclears 63 per cent, lymphocytes 35 per cent, monocytes 2 per cent. On March 25, 250 c.c. citrated blood were given. The stool examination was negative. Fragility at beginning hemolysis was 0.48 per cent and at complete hemolysis was 0.36 per cent. March 27 and 29, 250 c.c. citrated blood were given. On March 27, hemoglobin was 45 per cent, red blood cells 2,660,000, white blood cells 13,500, polymorphonuclears 78 per cent, lymphocytes 21 per cent, monocytes 1 per cent. On March 29, hemoglobin was 46 per cent, red blood cells 2,680,000, white blood cells 8,200, polymorphonuclears 75 per cent, lymphocytes 24 per cent, monocytes 1 per cent. Operation was on April 2, 1946. Citrated whole blood (250 c.c.) was given April 3, 4, 6, and 9. On April 3, hemoglobin was 50 per cent, red blood cells 2,750,000, white blood cells 8,800, polymorphonuclears 69 per cent, lymphocytes 30 per cent, monocytes 1 per cent. On April 4, hemoglobin was 68 per cent, red blood cells 3,530,000, white blood cells 15,700, polymorphonuclears 90 per cent, lymphocytes 6 per cent, monocytes 1 per cent, basophiles 3 per cent. On April 6 fragility at beginning hemolysis was 0.40 per cent and at complete hemolysis was 0.32 per cent. April 9 hemoglobin was 69 per cent and the red blood cells were 3,820,000.

Synopsis of Operative Procedure, April 2, 1946.—A subcostal incision was made parallel to the costal margin in the left upper quadrant, through which the abdomen was explored. The spleen was found to be about twice normal size. There were some adhesions to adjacent viscera at its upper extremity but not to the diaphragm. It was delivered through the incision after separating the adhesions, and was separated from its proximity to the stomach and pancreas. It was gently compressed to reduce its engorgement and the splenic artery was first ligated with #1 chromic sutures. The venous radicals were then ligated in like manner and there was no bleeding at the site of splenectomy. The appendix was then removed.

Pathologist's Report by Dr. Oscar B. Hunter.—Grossly, the spleen is covered by a slate gray capsule which is smooth, but the underlying splenic tissue is somewhat wrinkled. It is fairly firm and on section cuts with slightly increased resistance, revealing a red splenic pulp in which are found numerous tiny, grayish-white miliary lesions. No evidence of infarction, abscess, or other specific pathology is noted.

Microscopic Examination.—Sections from the spleen reveal considerable thickening of the capsule and a number of fibrous tissue trabeculae extending into the splenic pulp. The latter is completely filled with numerous red cells and the splenic corpuscles are compressed and have lost much of their typical appearance, although in some instances there is a remnant of the corpuscle present. The sinuses are almost completely devoid of contents. Throughout the spleen there are numerous areas showing some hemosiderin deposit, but a true marked hemosiderosis is not present. The vessels show some thickening of their walls in some areas and in a number of instances contain varying amounts of coagulated serum, typical of familial hemolytic icterus.

CASE 2.—This patient was a first cousin (maternal) of the first patient. The disease was diagnosed here as well.

S. G., a 5-year-old white girl of German-American parentage, had a chief complaint of fever (102.8° F.), anorexia, and running nose. The father was living and well; the mother had splenectomy for familial hemolytic anemia three years previously; the maternal grandmother and great-grandmother had anemia and jaundice, the maternal grandmother was still living; the patient had no brothers or sisters. Past history was negative except for constipation.

Present Illness.—April 18, 1946, the patient complained of anorexia, fever, and running nose. Nosebleeds were of unexplained origin. The patient was well up to this time. She had infrequent abdominal pains. The skin was always sallow. The spleen was palpable to within three fingerbreadths below the costal margin in the nipple line. The patient was slightly undernourished but otherwise normal.

Listed below are dates of transfusions and data obtained from laboratory reports, etc.:

On April 19, 1946, hemoglobin was 8.1 Gm. (48 per cent), red blood cells 2,450,000, white blood cells 6,700, polymorphonuclears 46 per cent, lymphocytes 48 per cent, monocytes 5 per cent, eosinophiles 1 per cent. There was considerable anisocytosis and eccentric achromia, many microcytes, few poikilocytes, many cells showing marked polychromatophilia, no basophilic stippling or nucleated red blood cells with marked degree of anemia, microcytic hypochromic type, with tendency to leucopenia. Blood picture was of congenital hemolytic icterus. Fragility at beginning hemolysis was 0.48 per cent and at complete hemolysis was 9.42 per cent. The icterus index was 75. Van den Bergh direct reaction was negative, the indirect was 2.0 mg. per 100 c.c. On April 21, 23, 25, 29, and 30, 250 c.c. citrated blood were given. On April 21 hemoglobin was 40 per cent, red blood cells 2,290,000, white blood cells 6,600, polymorphonuclears 44 per cent, lymphocytes 50 per cent, monocytes 4 per cent, eosinophiles 1 per cent, basophiles 1 per cent. On April 23, hemoglobin was 51 per cent, red blood cells 2,870,000, white blood cells 6,500, polymorphonuclears 58 per cent, lymphocytes 39 per cent, monocytes 2 per cent, eosinophiles 1 per cent. On April 25, hemoglobin was 65 per cent, red blood cells 3,670,000, white blood cells 7,200, polymorphonuclears 59 per cent, lymphocytes 38 per cent, monocytes 2 per cent, eosinophiles 1 per cent. Operation was on April 29. On April 30,

hemoglobin was 72 per cent, red blood cells 3,710,000, white blood cells 27,500, polymorphonuclears 89 per cent, lymphocytes 10 per cent, monocytes 1 per cent. On May 4, hemoglobin was 75 per cent, red blood cells 3,910,000, white blood cells 10,400, polymorphonuclears 80 per cent, lymphocytes 18 per cent, monocytes 1 per cent, basophiles 1 per cent, occasional microcytes, poikilocytes. The icterus index was 24. The Van den Bergh direct reaction was immediate positive, the indirect was 3.1 mg. per 100 c.c. On May 6, the icterus index was 10 and the Van den Bergh direct reaction was negative, indirect, 1.1 mg. per 100 c.c.

Synopsis of Operative Procedure, April 29, 1946.—A transverse incision was made in the upper left quadrant through which the abdomen was explored. The findings were essentially negative except for a markedly enlarged spleen which was easily mobilized. The spleen was about three times normal size. Some fine peritoneal adhesions were separated. The pedicle was exposed, the vessels clamped, divided and ligated separately with #1 chromic double suture following which a sponge was placed in oozing area until the appendix was removed.

Pathologist's Report by Dr. Oscar B. Hunter.—Grossly, the spleen is considerably enlarged, measuring 12 cm. in length by 9 cm. in width by 6 cm. in thickness and weighing 217 grams. The capsule is slate gray in color after fixation and is definitely thickened. Sections through the spleen reveal a firm splenic pulp. It is quite meaty in consistency and numerous enlarged follicles are noted. No gross evidence of infarction or involvement other than splenomegaly is noted.

Sections from the spleen reveal some thickening of the capsule, and characteristic fibrous tissue trabeculae extending into the splenic pulp. Some areas show increased fibrosis throughout the sections studied and in most parts of the spleen the pulp is completely filled with red cells. The splenic corpuscles are fairly characteristic in some instances, showing a typical follicular arrangement of the lymphoid cells, while in others the lymphocytes are more or less scattered. The sinuses in most instances are thickened and some contain small amounts of blood. The picture is that of a spleen in a case of congenital hemolytic icterus.

These two patients recovered rapidly and mark but one generation of the disease in the family. There was no evidence of paternal stigma. By pursuing the family history we have assembled the following data which we present as evidence that four known generations of this family have suffered from the disease.

1. The mother of our second patient, J. G., was operated on at the George Washington Hospital by Dr. Stewart M. Grayson in 1943, when a diagnosis of acholuric jaundice was made and a splenectomy performed. This is a second generation.

2. In a communication from this family's physician, Dr. Sarah Peyton, verification was received that Mrs. C., the mother of Mrs. J. G., and the maternal grandmother of B. S. and S. G., has the disease, with the concomitant findings of cholecystitis with cholelithiasis, the usual complication of the disease in older people. This is the third generation.

3. Although complete data cannot be assembled for the fourth generation, we have the history from communications from Mrs. C and the family physician, Dr. Sarah Peyton, in which they state that the maternal great-grandmother had fever and jaundice of marked degree at times. The jaundice and fever varied in intensity as she underwent a series of crises in the disease. She was known to have had the disease from early childhood and at death the undertaker noted that, "she had the smallest amount of blood I have ever seen."

Two main indications for early splenectomy as the primary treatment for this disease are: (1) the high incidence of cholelithiasis; and (2) the prevention of hemolysis and blood destruction, as marked improvement has been observed in those upon whom splenectomy was performed. Barber,[3] in a series of cases in one family, confirmed the finding that the anemia and jaundice disappeared rapidly, though the fragility of the red blood cells continued for an indefinite time following the splenectomy.

CONCLUSIONS

1. Confirming previous observations, definite evidence of the part heredity plays in this disease has been shown by its appearance in two first cousins (splenectomy), their aunt (splenectomy), their grandmother (icterus-anemia) and their great-grandmother (icterus-anemia), all maternal, representing four generations of the same family.

2. Blood studies on all members of a family are indicated when the diagnosis has been made in any one.

3. Preoperative transfusions give no sustained improvement and are palliative.

4. Early splenectomy, followed by transfusions, promotes convalescence and sustained improvement.

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AN UNUSUAL ERUPTIVE FEVER INVOLVING THE SKIN AND MUCOUS MEMBRANES

Its Relation to and the Status of the So-Called Stevens-Johnson Disease

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IT IS our purpose to present a case of an unusual systemic infection with an eruptive fever involving the skin, eyes, lips, buccal cavity, and urethral meatus. In addition, we shall discuss its relation to a small group of similar, previously reported cases, with particular reference to those in the category of the so-called Stevens-Johnson disease.

Full credit has been given to von Hebra[1] (1866) for describing the erythema multiforme exudativum group, although Bazin[2] (according to Keil[3]) was the first to recognize the occurrence of lesions in the mouth and the prodromal constitutional symptoms in the vesiculobullous type of erythema multiforme exudativum. Undoubtedly von Hebra[1] also underestimated the attendant severity of a small number of these cases. Early reports with involvement of the eye include those of Fuchs,[4] Hanke,[5] and Bergmeister.[6] Hanke's case terminated fatally. Then, in 1922, Stevens and Johnson[7] cited two cases of a "new eruptive fever associated with stomatitis and ophthalmia;" the skin eruption here is described as "extraordinary" and "unlike any hitherto described." With the appearance of this paper, new interest was aroused in the erythema multiforme group, especially in America. For this Stevens and Johnson are to be given full credit, although they were mistaken as to the "newness" of their report. Following this, a wide variety of cases (but a small number) has been noted in the literature as Stevens-Johnson disease. Almost at once a controversy arose and still exists concerning the usefulness of and necessity for the new term. There are those who prefer to regard Stevens-Johnson disease as a type of erythema multiforme exudativum (Hebra) rather than as a distinct entity. The authors hold the first opinion for reasons which will be discussed later in this paper. In this belief, we are in agreement with Fletcher and Harris,[8] Weisberg and Rosen,[9] Keil[3] and others. Givner and Ageloff,[10, 11] Murphy,[12] Patz,[13] and Nellen,[14] among others, hold the opposing view. The following case report will be of interest to all, however, because of its comparative rarity.

E. W. L., an 8-year-old boy of Jewish parentage, was admitted to the hospital on Dec. 19, 1946, with the chief complaint of a sore mouth. Five days before admission, the patient suddenly complained of malaise, nausea, sore throat, and pain in the stomach. The oral temperature was 102° F. The throat and buccal mucous membranes appeared inflamed. A physician prescribed a mixture of aspirin, phenacetin, and caffeine. The next day a mild, infrequent, nonproductive cough appeared, together with severe anorexia and

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pain on swallowing. In the succeeding forty-eight hours, all the symptoms persisted, with only slight improvement in the patient's condition. During this period the patient vomited several times, the contents being either mucus or food. The temperature remained elevated between 100° and 101° F. A mucoid nasal discharge, which had been present at intervals for the previous two months, increased in severity. On the day prior to admission, the temperature quickly climbed to 104.6° F.; the boy became somewhat toxic and an increased respiratory rate was noted. Oral penicillin (50,000 units) every two hours and nose drops were begun. That evening the patient was first seen by one of us (R. A. S.) in consultation. No significant new findings were observed except for swollen lips and small hemorrhagic areas on the hard palate and buccal mucous membranes. The patient was given 6 c.c. of gamma globulin intramuscularly, because of the possibility of invasion by hemorrhagic measles. Examination of the blood by a private laboratory showed a hemoglobin of 70 per cent, a red-cell count of 5,940,000 and a white-cell count of 11,150 with 13 per cent adult neutrophiles, 46 per cent young forms, 40 per cent lymphocytes, and 1 per cent monocytes. The platelet count was 248,000. The patient was admitted to the hospital on the following day with the diagnosis of an acute virus infection, etiology to be determined.

The past history revealed a fever of undetermined origin at the age of 3 years, with chicken pox two years later. The boy had been immunized against diphtheria, smallpox, tetanus, pertussis, and typhoid fever. Two months prior to the present episode, the patient recovered from infectious mononucleosis. There was no known recent exposure to measles, although a neighboring child had mumps "several weeks" past. However, there was a history of contact two weeks prior to this illness with three dogs, two of which were ill with fever and cough; and were subsequently diagnosed by a veterinarian as a "streptococcus sore throat," although no cultures were taken. The family history was noncontributory.

Physical examination revealed a patient who appeared acutely ill, complaining bitterly of a sore mouth and photophobia. There was a moderately severe conjunctivitis, but no ocular discharge. The nasal mucosa were distinctly swollen and congested; a mucoid nasal discharge was present. The lips were dry and swollen. On the buccal mucous membranes, including the hard and soft palate, were many small, whitish areas of necrotic mucous membrane. The pharynx was injected; a small amount of mucopurulent exudate was seen in the throat. The tongue was dry and coated white. The anterior and posterior cervical lymph nodes were enlarged; the axillary and inguinal nodes were small and shotty. Examination of the chest revealed many medium and coarse dry inspiratory râles over the right posterior hemithorax from the fourth dorsal vertebra downward; the percussion note in this area was hyporesonant, with increased breath sounds. The spleen was not palpable. There was no hepatomegaly. On the skin of the volar and dorsal surface of the right hand were seven erythematous papules; on the left knee were several minute vesicles surrounded by a rim of erythema. The rectal temperature was 104.8° F., the pulse 140, and the respirations 38 per minute.

Examination of the blood showed hemoglobin of 11.5 Gm., red-cell count of 4,620,000 and a white-cell count of 13,000 with 85 per cent neutrophiles (of which half were young forms) 10 per cent lymphocytes and 5 per cent monocytes. A routine urinalysis disclosed a faint trace of albumin, with a few white cells and bacteria in the sediment. A Rumpel-Leede test was negative. Blood cultures were sterile. A nasopharyngeal smear showed gram-positive cocci and diplococci; the culture revealed hemolytic streptococci, pneumococci, and *Staphylococcus albus*. A conjunctival smear and culture were negative. A portable chest x-ray film was negative.

Penicillin by intramuscular route in the dose of 25,000 units every three hours was begun at once owing to the possibility of a secondary infection as evidenced, for example, by the marked increase in neutrophiles. In addition, general supportive care was ordered, including frequent use of mouthwashes, intravenous fluids, and blood transfusions.

On the second day the patient seemed worse. The temperature, after an early morning drop to 100.5° F. (rectally), rose to a maximum of 106.2° F. (rectally). At this time the boy was alternately drowsy and very irritable. Examination revealed an increase in the extent of the skin lesions. Present on the posterior aspect of both upper thighs, anterior surface of the left thigh, dorsal surface of the left arm and right elbow were numerous small (1 to 2 mm.) vesicles, containing a clear fluid, surrounded by a rim of erythema varying in size from 0.2 mm. to over 1 cm. The skin about the urethral meatus was inflamed, but no discharge was evident. Both lips, particularly the lower, showed extensive, raw, bleeding areas with crust formation. There was no significant change in the oral lesions. A right subconjunctival hemorrhage was present; the conjunctivitis was more severe. The patient refused to take any food or fluids by mouth because of the marked soreness of the mouth and throat. His cough increased in severity and frequency. Fortunately, the temperature dropped to 99° F. by evening. In view of the character of the lesions, a diagnosis of herpes stomatitis was suggested, with spread of the herpes virus throughout the body, probably through the blood stream. Accordingly, specimens of saliva were sent to the Virus Diagnostic Research Laboratory of the Children's Hospital, Philadelphia, where tests were performed on rabbit corneas and in chick embryos. These, however, yielded no evidence of the herpes virus. Blood sent for virus neutralization tests eventually proved also to be negative. It was impossible to obtain fluid from the vesicles because of their minute size.

During the first four days, feedings were almost entirely by the parenteral route. Slowly the patient accepted increasingly larger amounts of nourishment orally so that all intravenous fluids were discontinued on the eighth day. Local eye therapy included frequent boric acid compresses and the instillation of one drop of colloidal silver solution (10 per cent) three times daily. With this, the conjunctivitis steadily improved, finally disappeared by the tenth day. After the second day, the rectal temperature rose to 103° F. on only one occasion (third day) and then slowly subsided by lysis, remaining less than 100° F. (rectally) from the fifteenth day until discharge.

On the third day, the skin lesions began to dry, the lips appeared swollen but dry with some areas of scaling and other spots where the surface epithelium was eroded. The whitish necrotic areas in the mouth gradually sloughed, leaving raw areas which bled easily. By the eighth day brown scabs surrounded by an area of erythema had formed at the site of all the formerly vesicular lesions. The oral lesions had almost entirely cleared, except for an ulcer on the frenum of the tongue. The lips were much less swollen, with a few small areas of superficial epithelial erosion present. The cough was gone. Penicillin was discontinued on the tenth day, a total of 1,625,000 units having been given. Later (eleventh day), the scabs fell, leaving pinkish-brown spots which gradually faded. A white cell count on the thirteenth day was 10,500 with 67 per cent neutrophiles (of which 91 per cent were filamented) 29 per cent lymphocytes and 4 per cent monocytes. The patient was discharged on the eighteenth day apparently in perfect health.

It is of interest here to note that, although we were unable to implicate the herpes virus as the causative agent in this patient's illness, we are not the first to suggest an etiologic relationship between herpes simplex and erythema multiforme. In America, Anderson[15] (and before him Forman and Whitwell[16] in England) had suggested such an association.

The history of contact with sick dogs has not been reported previously, to our knowledge, in this group. Careful questioning in future cases may bring to light the importance of animal contact. It is well known, moreover, that children are likely to have much closer association with animals than have adults. This may be the cause of the greater incidence of severe forms of erythema multiforme exudativum (Hebra) in children.

The early use of penicillin in adequate dosage may have been of value in preventing the complications of secondary infection. We do not believe it had any direct effect on the illness. Goldfarb[17] noted that decided improvement in his case seemed to be related in time to the use of penicillin, especially locally.

DISCUSSION

In our attempt to diagnose this case, our attention was soon centered on the erythema multiforme exsudativum (Hebra) group and then to the consideration of the so-called Stevens-Johnson disease. According to Keil,[3] the cutaneous lesions of erythema multiforme exudativum (Hebra) can be conveniently classified, for clinical purposes, into the maculopapular and the vesiculobullous types, although, it must be cautioned, both variants may occur in the same patient simultaneously, in subsequent crops, or in later recurrences. In an excellent paper Fletcher and Harris[8] set down the criteria for the diagnosis of erythema multiforme exudativum (Hebra)—bullous type as follows:

1. Multiform erythematous skin lesions.
2. Bullous formation on the skin or mucous membranes.
3. Constitutional symptoms compatible with an acute infectious disease.

If we substitute the word "vesicle" for "bullous," the relation to this case is manifest. Fletcher and Harris[8] classify individual cases, moreover, into mild, moderately severe, severe, and grave forms.

Only on search of the literature of Stevens-Johnson disease did we realize with how vague an entity we were dealing. The differences in the material described are quite extreme and the criteria laid down by the various authors for its diagnosis are so conflicting that it makes one wonder whether Stevens-Johnson disease is a distinct entity. This confusion has arisen, we believe, partly from indiscriminate efforts to extend the scope of the disease as defined by Stevens and Johnson[7] themselves; and partly from the belief that the term Stevens-Johnson disease is synonymous with erythema multiforme exudativum (Hebra)—vesiculobullous type, or by some, with the entire erythema multiforme group. There is no question that Stevens and Johnson described a serious form of erythema multiforme, a form which only infrequently occurs and which had not been well recognized before their paper. This is not sufficient reason, however, to call it a distinct entity.

It is our hypothesis with regard to much of the erythema multiforme group that we are dealing with an infection by organisms of a similar type, probably viral in nature, and with a hematogenous spread. One must consider here in parallel the known example of measles which exhibits definite, though at times atypical, cutaneous lesions. The multiform cutaneous lesions of the group under discussion may be, in truth, merely manifestations of the same systemic infection differing only because of other factors involved, such as the virulence of the invader, the degree of resistance of the host, and others, presently known and unknown. Morphologic classifications of disease will be, we trust, only temporary standards. Thus, in the inorganic class of noxious agents, it is well known that the cutaneous lesions of chronic arsenic poisoning may be of almost any type.

As a baseline for further discussion, we shall summarize the two cases presented by Stevens and Johnson and attempt to point out the particular emphasis they placed on certain aspects of their cases. Both cases occurred in young boys, both had a high and prolonged fever, and both a purulent conjunctivitis. (This last is considered important not only by Stevens and Johnson, but also by later investigators). It is the skin eruption, however, which highlights the report, being described as "extraordinary" and "unlike any hitherto described." The rash appeared first on the back of the neck and chest, spreading to the face and extremities but not to the scalp during a period of eighteen days. The lesions were first dark red oval macules varying from 0.5 cm. to 2 cm. in their longest diameter and without areolae. In a few days these macules became brownish purple papules, some of which acquired yellow, dry, necrotic centers. Vesicles and pustules were absent. Later, the lesions changed to dark brown, horny, thick scales with raised, papery edges. (This change was considered by the authors to be of diagnostic significance). From the fourth week, the scales dropped off, leaving faint pigmented areas without pitting or scarring. We contrast this with the exanthem and absence of a purulent conjunctivitis in our case.

Concerning the oral lesions, it is recorded in Case 1 that the oral mucous membranes were inflamed and showed small bullous lesions which rapidly broke down, leaving a raw and angry surface. No mention is made of this

aspect again in the entire case report. In Case 2 it is recorded that when the patient was at another hospital the mucous membrane of the mouth was practically exfoliated. On the twenty-third day, when Stevens and Johnson apparently first saw the patient, no statement is made concerning any oral lesions. From this we conclude that Stevens and Johnson emphasized only the presence of a stomatitis, not of a particular type, as bullous or membranous. Moreover, in the summary of their paper, we find no statement of bullous lesions, whether on the skin or mucous membranes. We mention this point particularly because of the impression obtained on reading later papers (as Kove,[18] Murphy,[12] and Nellen[14]), that the presence of a bullous or vesicular lesion is a cardinal factor in the diagnosis of Stevens-Johnson disease. Our viewpoint is substantiated by the fact that in Wheeler's[19] case, which was seen by Stevens himself, no bullae were noted. Again, it is the exanthem and not the oral lesions which seem to have been the striking element. Wheeler[19] states, "Scattered over the body were brownish spots unlike anything I had seen."

We agree with Keil[3] that the symptoms described would place the so-called Stevens-Johnson disease within the category of the maculopapular type of erythema multiforme exudativum (Hebra). Ginandes,[20] in an early paper declares, "I am not certain that the differences are sufficiently striking to warrant such a separation [i.e. to regard Stevens-Johnson disease as a separate entity—*author's note*]. One finds, rather, sufficient resemblance in all these cases to believe they more probably belong to the same group."

With regard to the degree of ocular involvement, there are already several conflicting opinions. Duke-Elder[21] regards Stevens-Johnson disease as a form of ocular erythema multiforme with a purulent conjunctivitis. Jones, Talbot, and King[22] are in agreement and express the opinion that Stevens-Johnson disease should be reserved for those patients presenting a purulent conjunctivitis, stomatitis, and a cutaneous rash without the formation of an (ocular) membrane. This would apparently exclude such cases as those of Ginandes,[20] Patz,[13] Givner and Ageloff,[11] (Case 1), Rutherford,[23] and Kove[18] (Case 2). In addition, what are we to do with the reports of Grossman[24] (Cases 1, 4, and 5), and Umiker and Crofoot,[25] where only a catarrhal conjunctivitis was present? Or those of Levy[26] and Grossman[24] (Case 6) with no ocular involvement? Are these "true" Stevens-Johnson disease? In contrast to Duke-Elder,[21] Erger[27] states, "Numerous degrees of eye involvement have been reported, ranging from simple catarrhal conjunctivitis to ocular destruction."

We find no unanimity of opinion in regard to the cutaneous lesions, either, in spite of the emphasis placed by Stevens and Johnson on this point. Descriptions have ranged from no exanthem at all (Kove,[18] Case 1 and Wentz and Seiple,[28] Case 1) to unusual combinations of macules, papules, vesicles, petechiae, and bullae. Erger[27] remarks, in contrast, that the cutaneous lesions are more likely to be uniform than multiform. Grossman[24] described four cases, in which the cutaneous manifestations, vesicular and bullous in nature, were confined to the penis and lips.

It would appear, then, that the effort to have the small, round peg of "Stevens-Johnson" disease fill the large, square hole of erythema multiforme

exudativum (Hebra) has resulted only in confusion. If the term Stevens-Johnson disease is to be used at all, whether one considers it a distinct entity or only a variant of erythema multiforme, the diagnosis should be strictly reserved for these cases, otherwise unclassifiable, presenting: (1) constitutional symptoms resembling an acute infectious disease; (2) multiform erythematous skin lesions, predominantly of a maculopapular nature; (3) a purulent conjunctivitis without the formation of an ocular membrane; (4) a stomatitis.

The differential diagnosis rests mainly among hemorrhagic measles, smallpox, syphilis, dermatitis herpetiformis, pemphigus, agranulocytosis, septicemia, and Vincent's angina.

SUMMARY

A case of an unusual eruptive fever associated with conjunctivitis, stomatitis, nasopharyngitis, and urethral meatitis is presented. A history of contact with sick dogs is reported, apparently for the first time, in this group of cases. Studies to incriminate the herpes virus as the etiologic agent were negative. The status of the so-called Stevens-Johnson disease is reviewed and defined more clearly. The conclusion is reached that Stevens-Johnson disease is only a form of erythema multiforme exudativum (Hebra) and not a distinct entity. The hypothesis is put forward that, with regard to much of the erythema multiforme group, that we are dealing with an infection by organisms of a similar type, probably viral in nature. The multiform cutaneous lesions may be, in truth, merely manifestations of the same systemic infection.

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CONGENITAL HYPERTROPHIC STENOSIS OF THE DUODENUM

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A CONDITION best listed under the nomenclature of congenital hypertrophic stenosis of the duodenum has been encountered in two infants, one of whom was seen twelve years ago, and the other recently. A fairly thorough search of the literature, with the assistance of the staff of the Library of Los Angeles County Medical Association, has failed to reveal any previous report of the condition. Several forms of duodenal obstruction at birth or in early infancy have been discussed, but none of this particular variety, in which the findings are so strikingly similar to those ordinarily encountered at the pylorus, has been mentioned.

Each of the patients discussed in this paper had a fusiform swelling about 1¼ inch in length, whitish, smooth, composed of abnormally hypertrophied muscle, and of a consistency halfway between gelatine and cartilage, the duodenal wall being thickened to a depth of 3/16 inch or so, the lumen being constricted until the edematous mucosa was bunched up into a practically impassable mass. All of this is characteristic of the fairly common stenosis of the pylorus, but in these cases it was confined to the first portion of the duodenum, with no encroachment on the pylorus.

Both of these patients were male infants. Both were treated by longitudinal myotomy (Rammstedt) down to mucosa; in both cases the mucosa was inadvertently opened and repaired by suture; and in both cases the babies survived and had no more obstructive symptoms.

The chief anatomic difference between the two infants was that the first one had a constriction at the midportion of the tumor, as if a band had at one time almost completely encircled it, this constriction being practically the full depth of the tumorous bowel wall. It was at this thin place that the mucosa was entered during surgery.

The first infant was seen in 1935, at about 4 weeks of age. Normal at birth, he began vomiting at 10 days of age, but, despite increasing emesis, weighed the same as he had at birth at 3 weeks of age, and continued to gain to 1 pound, 6 ounces over birth weight when operated upon at 6 weeks of age. Observation was not alert enough at this time to note whether there was any bile in the vomitus or not. Operation was done because thick cereal feeding and atropine had been unavailing in stopping the projectile vomiting, and because there were large visible peristaltic waves.

The second patient, seen in 1947, arrived at surgery at 4 weeks of age, after a very confusing course. A firstborn infant, delivered at term by a very difficult breech extraction, he was in severe shock and depression at birth, with right facial palsy, partial third nerve paralysis, and presumptive cerebral edema.

He rallied well, however, and although the paralysis persisted, arousing suspicion of spasticity, and an occipital cephalhematoma and hemorrhage into the sheath of the right sternomastoid muscle developed, he took his bottle well and had gained back to birth weight at 2 weeks of age, when vomiting began. Concentrated feedings were tried without improvement. Phenobarbital was used, but

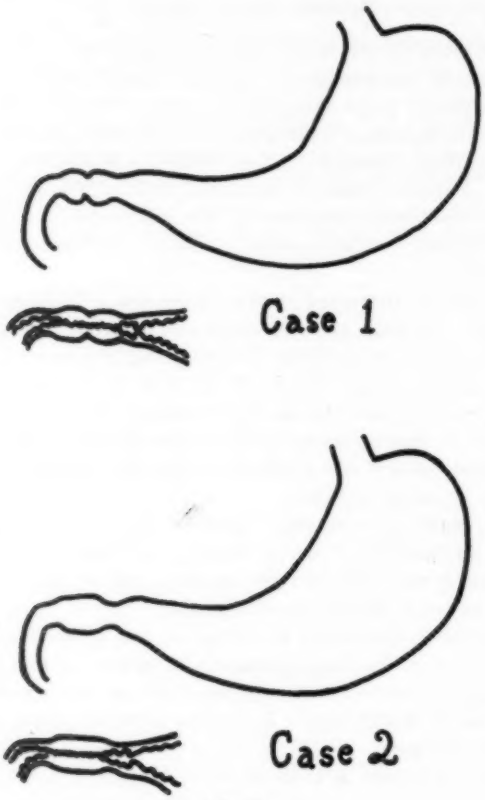

Fig. 1.

its only effect was to throw him into profound stupor bordering on coma, which lasted for several days after it was discontinued. The vomiting became rapidly worse until it was practically total when the infant reached 3 weeks of age. Vomited material seemed to be stained yellowish at times. There was never any distention. There were no peristaltic waves visible at any time, nor was a tumor felt, although it was noted verbally at one time that up under the liver edge something harder than normal and rather pecan-shaped seemed to meet the examining fingertips. X-ray of the abdomen in a vertical position showed

no pools of fluid in intestinal loops and very little gas below the stomach. A little normal stool came through on suppository or enema for several days. Because of lack of evidence of obstruction, neurosurgical consultation was obtained. Subdural hematoma was ruled out and it was the opinion of the neurosurgeon that little if any severe brain damage had been done, and that this would probably clear up in time. Meanwhile, the baby was being sustained on intravenous amigen and glucose, and remained in surprisingly good hydration and general condition. The issue was determined as calling for surgical exploration when the baby, at 4 weeks of age, began to pass dark stools which quickly became tarry mucus only.

Case Reports

OMPHALOCELE

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A SMALL umbilical hernia is a condition that is frequently encountered in infancy. Large hernias of the umbilical cord containing several loops of intestine with or without other abdominal organs are quite rare, however. Such large hernias, called omphaloceles, or umbilical eventrations, occur approximately once in every 5,000 to 10,000 births. As would be expected, unless the eventration is surgically repaired soon after birth, the mortality rate is almost 100 per cent. In the largest series of infants treated surgically,[1] the mortality rate was 49 per cent.

Jarcho[2] extensively reviewed the literature on omphalocele up to 1937 and described a patient (in whom the hernial sac contained liver) who was successfully treated by surgery. In 1940, Gross and Blodgett[1] reported twenty-two patients with the condition, ten of whom were still alive at the time of publication of their report. None of their patients lived, however, when the hernial sac had ruptured and peritonitis had occurred. A search of the literature likewise revealed no reported survivals following rupture of the sac. The following report on a patient with umbilical eventration who lived following surgery is presented because of the severe complications that occurred and the method of treatment that was used.

CASE REPORT

Baby A, the second child of a 21-year-old white woman, was delivered by low forceps at term after a labor of eight hours. The baby weighed 6½ pounds and had a defect 4.5 cm. in diameter in the abdominal wall in the region of the umbilicus, through which about two feet of the small bowel, cecum, and part of the stomach had passed (Fig. 1). No skin or covering was present over this defect. During the process of delivery the peritoneal covering of the hernial sac had apparently ruptured and the intestines had become exposed so that they were contaminated by the mother's perineum. Immediately following completion of the delivery, the baby was put in a sterile sheet and the intestines were covered with sterile packs soaked in physiologic saline solution. Approximately two hours later the intestines were replaced into the abdominal cavity and the defect was closed surgically in three layers. No immediate respiratory distress was noticed following the replacement of the intestines into the abdominal cavity and the baby was returned to the ward in good condition.

The patient was kept in an incubator for the first few days and was given oxygen continuously as well as 30,000 units of penicillin intramuscularly every three hours, since the intestines were known to have been contaminated during the delivery. Beginning at twelve hours of age, water was offered by bottle every three hours. The child nursed well, but several minutes after being fed it regurgitated bile-stained material and abdominal distention began to occur. In view of the apparent partial intestinal obstruction, the minimum daily fluid requirements were thereafter administered parenterally. Because regurgitation

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Fig. 1.—Picture of patient at birth showing 4.5 cm. umbilical defect with stomach, small bowel, and cecum protruding.

Fig. 2.—X-ray of patient taken on third day of life showing marked distention of stomach and several loops of bowel in left lower quadrant.

of bile-stained material following oral feedings persisted, x-rays were taken on the third day of life. These revealed marked distention of the stomach and several large loops of bowel in the left lower quadrant (Fig. 2). Barium given orally remained in the stomach after six hours, although some seemed to appear in the small bowel. Wangensteen gastric suction was instituted in view of the x-ray findings and parenteral fluid therapy was continued. Intravenous plasma was given approximately every other day in addition to subcutaneous solutions.

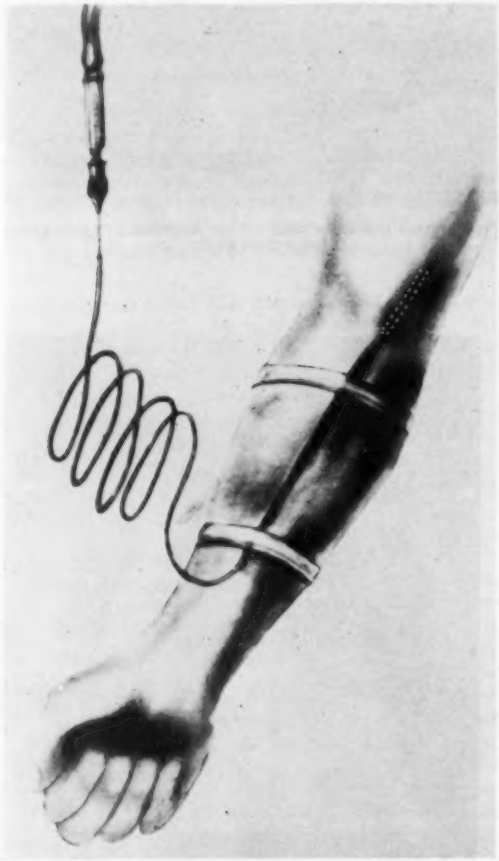

Fig. 3.—Drawing illustrating use of ureteral catheter for constant intravenous transfusion. After cut-down on vein, catheter is inserted several centimeters, as shown by dotted lines; other end of catheter is connected to intravenous tubing by No. 23 needle. Note length of catheter permitting free movement of extremity.

In spite of continuous gastric suction and parenteral fluids, the baby's abdomen remained distended. On the sixth day of life barium was again given by mouth and followed under the fluoroscope in an attempt to find an area of obstruction. The barium remained in the stomach for the most part, but some was seen to pass through the duodenum, jejunum, and into the left lower quadrant of the pelvis, beyond which no barium would pass.

In view of the definite evidence of obstruction by x-ray, and since the baby already had one known congenital defect, it was thought that further defects such as intestinal atresia or stenosis might be present. Accordingly, on the ninth day of life the baby's abdomen was explored surgically under ether anesthesia. Upon opening the peritoneum a generalized peritonitis was encountered. Loops of small bowel were adhered together and several large

Fig. 4.—Picture of patient one month following discharge from hospital. Defect is well healed.

abscesses were present in the roots of the mesentery; one abscess was causing intestinal obstruction in the left lower quadrant. The abscesses were incised and drained and the abdomen was closed with difficulty using #36 steel wire and chromic catgut. The baby was returned to the ward in semishock.

For the next seven days following the abdominal exploration and drainage of the abscesses, the baby's condition was critical. It was obvious that the baby would have to be fed parenterally over a long period of time and so a cut-down was made on the right cubital vein and a #4 ureteral catheter was inserted 2½ inches up into the vein. The catheter was inserted this distance so as to offset any possibility of its coming out during the several

days that it was to remain in place. The catheter was taped securely to the arm and the baby was allowed to move the extremity at will (Fig. 3). During the next seven days the baby received plasma or whole blood through the catheter continuously, in addition to calculated amounts of 5 per cent glucose in saline or distilled water, vitamin B complex, ascorbic acid, vitamin K, and penicillin. Gastric suction was maintained for five postoperative days, after which time small amounts of glucose water were offered by bottle every two hours. Gradually the oral amount was increased as well as the time interval between feeding so that by eight days postoperatively the baby was taking 3 oz. of formula every three hours without regurgitation. Parenteral feedings were subsequently discontinued.

Postoperatively the abdominal incision broke down and became infected. This was treated satisfactorily at first with magnesium sulfate soaks and later with penicillin soaks. The baby was discharged from the hospital at 35 days of age in only fair nutritional condition, but he was eating well. On a standard formula, multiple vitamins, iron, and good care by the parents the baby improved remarkably in one month (Fig. 4). When last seen at 7 months of age the baby weighed 16½ pounds and was developing normally. Only a questionable defect was present in the anterior abdominal wall.

SUMMARY

1. Omphalocele of the umbilical cord occurs rarely and has a high mortality rate unless repaired early.

2. A successfully treated case of omphalocele which did not have a peritoneal covering is reported.

3. The case is remarkable because of the complicating mesenteric abscesses and peritonitis.

4. A method of continuous administration of intravenous fluids through a ureteral catheter is described.

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HEMANGIOMA OF THE LIVER CAUSING DEATH IN A NEWBORN INFANT

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RUPTURE of a hemangioma of the liver is seldom considered in the differential diagnosis of shock in the newborn. Indeed, the condition is rare. Shumacker,[1] in a review of hemangioma of the liver, presented only two cases affecting newborn infants: one occurred in a 7-day-old infant reported by Hammer,[2] and the second in a 3-day-old newborn infant reported by Kissinger.[3] No other cases have been reported in recent literature.

Cavernous hemangioma of the liver is described as the most common benign tumor of the liver, yet there are rarely any ill effects, it usually being an incidental finding at autopsy.[4] Moreover, it is more common in adults where it may occasionally produce hepatic enlargement. Montgomery[5] states that trauma to the abdomen may cause a rupture of the tumor and a serious hemorrhage. This may have been a factor in the following case.

CASE REPORT

H., a boy, was born at 11:05 P.M. on June 21, 1947. The mother had no antepartum abnormalities; her Kahn test was negative and the Rh factor positive. The labor was extremely long and was complicated by a transverse position of the presenting head with a midpelvic arrest. At birth the infant's respirations and cry were spontaneous and immediate and the general condition was good. He was a full-term baby, weighing 7 lb., 4 oz.

An examination at thirty-six hours after birth showed a newborn child who was apparently normal: the color was pink, the cry lusty, respirations normal, Moro reflex active, tonus good, and there were no anomalies.

The baby's condition was considered to be good until the nurse noted him to be unduly pale at 2 A.M. on June 24, when 51 hours of age. Respirations were slow but were of good depth and the baby cried loudly when spanked. A heat cradle was applied. A few minutes later the cry was weaker and he was placed in an incubator and oxygen given. By 3 A.M. the condition was critical. The skin and the mucous membranes were extremely pale. Respirations were gasping in nature, and there were long periods of apnea. The heart sounds were inaudible. Tonus was poor. The abdomen was flat and the wall slightly tense. The anterior fontanel was not bulging. The impression was that he had experienced a sudden massive internal hemorrhage with resulting anemia and shock. Because of the extremely long and difficult labor, a massive intracranial hemorrhage seemed likely. Vitamin K, one milligram, was given intramuscularly. An emergency blood typing and cross-matching and a complete blood count were requested. When the blood had been prepared, the condition was so grave that it seemed certain that death would result immediately if a venesection were done. The baby died at 6:33 A.M., four and one-half hours after the appearance of the first signs of illness and after 55½ hours of life.

The laboratory reports were: erythrocytes, 3,410,000; hemoglobin, 9.9 Gm. or 68 per cent; leucocytes, 11,750, 44 per cent being polymorphonuclear. No abnormal cells were found.

The post-mortem examination showed a well-developed and -nourished newborn infant with pale skin and slightly distended abdomen. The pleural and

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pericardial cavities were negative. Scattered petechial hemorrhages were found beneath the visceral pleura.

On opening the peritoneal cavity there was found an estimated 350 c.c. of old dark blood, some of which was clotted. The peritoneal surfaces were normal. The liver presented the most significant findings. It was determined to be the site of the hemorrhage and the source of the blood in the peritoneal cavity. On the inferior surface of the liver, posterior to the gall bladder, was a large clot of blood measuring 8 cm. in its greatest diameter. The edge of the clot was continuous with the substance of the liver, indicating that the clot was beneath the capsule. The liver was a pasty yellow color on cut section. The gall bladder was normal.

There were no other significant gross findings except 15 to 20 c.c. of old blood, which was found beneath the tentorium cerebelli.

Microscopic examination.—There was a rather large amount of hemorrhage throughout all sections of the lungs, and no evidence of an infectious process. Serial sections through the liver revealed a rather remarkable finding. There were a large number of blood islands which could be seen throughout the liver substance along with evidence of parenchymatous and fatty degeneration. At one portion at which the previously described clot was adhered to the liver was a large hemangioma with hemorrhage, necrosis, and thrombosis within the hemorrhagic areas adhered to the liver substance.

The anatomic diagnosis was: (1) hemorrhagic disease of the newborn, and (2) hemangioma of the liver with hemorrhage, necrosis, and thrombosis.

The cause of death was severe peritoneal hemorrhage due to rupture of a hemangioma of the liver.

CONCLUSIONS

A fatal case of rupture of a hemangioma of the liver in a 2-day-old infant is reported.

The rupture may have been initiated by trauma incident to a difficult labor and complicated by hemorrhagic disease of the newborn infant.

Rupture of a hemangioma of the liver is to be considered in the differential diagnosis in cases of internal hemorrhage in the newborn infant.

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CONGENITAL TUBERCULOSIS

A Review of the Disease With Report of a Case

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IT IS a generally accepted medical fact that, with the exception of syphilis, prenatal infection by placental transmission is relatively rare. There are, however, cases on record of prenatal or natal smallpox, chickenpox, measles, tuberculosis, typhoid fever, and pyogenic infections.

In 1938, Conrad[1] gave this definition of congenital tuberculosis: "Tuberculosis in which the infection occurs before birth by way of the blood stream, or at birth by the aspiration of tuberculous amniotic fluid or tuberculous matter present in the birth canal."

It would seem that for the infection to be truly congenital, all cases occurring from aspiration of infected material at the time of birth should be excluded, because this type of infection would more properly be classified as acquired tuberculosis. However, true congenital tuberculous infection of the fetus is possible by aspiration or inhalation of infected amniotic fluid in utero.

In reviewing the literature it is found that there is much debate on the question of which cases reported should be classified as true congenital tuberculosis. The explanation of such widespread disagreement probably lies in the fact that there has been no definite accepted definition of congenital tuberculosis. We would like to suggest that the following definition of congenital tuberculosis become generally accepted: "Tuberculosis in which the infection occurs before birth by way of the blood stream or by aspiration or ingestion of infected amniotic fluid in utero."

Those cases which result from aspiration of infected material at the time of birth might well be termed "tuberculosis neonatorum."

The first authentic case of congenital tuberculosis in the human being was reported in 1891 by Schmorl and Birch-Hirschfeld.[2] Since that time many others have been reported.

In 1914 Pehn and Chalier[3, 4] made an extensive study of congenital tuberculosis and accepted only fifty-one cases as definitely proved.

In 1922 Whiteman and Greene[5] reviewed the literature and found 113 authentic cases and 519 more or less doubtful cases. To these they added their own case and several others they found in the literature.

Horak[7] in 1927 stated that the literature revealed 114 authentic and 519 doubtful cases of hereditary tuberculosis.

Beitzke[6] in 1935 reviewed 100 cases and passed sixty-one as true congenital tuberculosis. His criteria of proof of congenital tuberculosis in the infant were that: (1) the tuberculous nature of the lesions in the infant must be proved; (2) a primary complex in the fetal liver is proof of the congenital nature of the tuberculous changes, since it can have arisen only from tubercle bacilli in the blood of the umbilical vein; (3) if there is no primary complex in the liver, the infection is congenital only if (a) tuberculous changes are found in the fetus in utero or at birth or a few days after birth, and (b) in a child who lives longer than a few days if extrauterine infection can be excluded with certainty, the child being immediately separated from the mother and kept in an environment free from tubercle bacilli.

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Hughesdon,[12] in 1946, tabulated and classified thirty-five cases of congenital tuberculosis reported in medical literature from 1935 to 1945, inclusive, and added four cases which were observed in a children's hospital in England.

In an editorial[13] in the *Journal of the American Medical Association*, June, 1947, reference is made to the fact that during the last seventy years, 115 proved cases of congenital tuberculosis have been described in the literature, including both cases in which pathologic lesions were present and those in which only a tuberculous bacillemia occurred.

The writer, quoting Hughesdon, points out that infection of the fetus may take place when the mother's tuberculous lesion is minimal or even undetectable by present methods of investigation. He also notes that this is consistent with the view that tuberculous bacillemia may occur at any time during a period of activity of an existing tuberculous focus, no matter how small.

Chester A. Stewart, writing in Brennemann's *Practice of Pediatrics*, comments on the French investigators' theory of transplacental transmission of the filtrable tuberculous ultravirus. He refers to the writings of Calmette and associates.[9] These writers feel that infection by this portal with the filtrable ultravirus may exceed 80 per cent of infants born to tuberculous mothers, and that nearly 60 per cent of the alleged newborn carriers of the ultravirus withstand this infection without immediate harm.

Many reasons for being skeptical as to this means of the transmission of the disease have been advanced by Thompson and Farbisher.[10]

Stewart concludes that, for the present, infections in utero with a tuberculous ultravirus probably should be looked upon as an interesting possibility requiring much further study before being accepted as an established fact; and that transplacental infection with either the mycobacterium tuberculosis or the ultravirus stage is probably relatively rare.

Buchanon[11] reported two cases of neonatal tuberculosis in 1946, but one of these was not truly congenital.

The reader is referred to the excellent treatise of Conrad[1] for a review of the literature until 1938.

CASE REPORT

CASE 1.—B. G. B., a 3 pound, one ounce, female, premature Negro infant, was born at home at 1 P.M. on June 9, 1946. The delivery was precipitate, the doctor arriving just as the baby was born. A time interval of approximately ten to fifteen minutes elapsed between the birth of the baby and its removal from the mother's room. The placenta was expressed and disposed of, since it was not remarkable.

The baby was admitted to the Employees' Hospital fifty-five minutes after birth, and was at no subsequent time in contact with the mother, since for the remainder of her life the baby remained in an incubator with only trained hospital personnel in attendance. The period of gestation was estimated at seven months.

The only significant finding in the family history was that the mother had been receiving antisyphilitic treatment before the baby was born.

On the initial physical examination the only findings were those of prematurity and some cyanosis of the palms and soles.

The admission diagnosis was: premature newborn infant.

Clinical Course.—Routine measures for premature infants were instituted, and the baby progressed satisfactorily until June 22, 1946, at which time a small abscess was noted on the right arm. This was aspirated on this day and incised and drained a day later. On June 27, the baby passed two stools with gross blood. On the following day she began to have a diarrhea and she passed four to six diarrheal stools a day for a week, some with blood. July 6 the stools were normal.

She was given ½ c.c. crude liver extract intramuscularly on July 2, 3, and 4.

Another abscess was noted on the lateral aspect of the right thigh July 9, from which a small amount of thick, yellow, blood-streaked pus was aspirated. It was then incised and drained. Culture of the pus showed *Bacillus coli.* The abscess drained for twenty-four hours and was reopened on July 12, at which time about two drachms of pus were evacuated. On July 22 the baby began to have diarrhea again and on this day she passed eight soft white stools. The next day, the day of death, she passed ten watery white stools and the abdomen became distended. She died at 7:55 P.M.

As previously recorded, the birth weight was 3 pounds, one ounce. The baby weighed 2 pounds, 15½ ounces, on each of the next four days. On the fifth day she weighed 3 pounds, ½ ounce, and the next day had regained her birth weight. From this time until three days before death her weight gain was steady. On the twenty-second day she weighed 3 pounds, 4 ounces; on the twenty-ninth day the weight was 3 pounds, 9 ounces, and on the thirty-fourth day she weighed 4 pounds. On the thirty-eighth day she weighed 4 pounds, 3½ ounces.

LABORATORY REPORT

Urine.—6/20/46 Negative except for occasional white blood cells.
7/15/46 Negative except for trace of albumin.

Serology.—7/3/46 Negative Kahn.

	Date	*Hgb. (%)*	*W.B.C.*	*R.B.C.*	*Differential*
Blood.—	6/10/46	80	12,500	4,425,000	J-4, St.-5, P-40, L-47, M-4
	6/27/46	60	13,000	2,700,000	
	6/28/46	55	5,500	2,400,000	
	7/ 1/46	45	6,000	2,200,000	
	7/ 3/46	50	6,000	2,000,000	
	7/ 6/46	40	8,750	1,600,000	
	7/ 8/46	55	9,250	2,500,000	
	7/10/46	55	14,500	2,675,000	
	7/11/46	65	12,500	3,400,000	
	7/13/46	55	17,250	2,225,000	
	7/15/46	55	14,000	2,300,000	
	7/20/46	50	16,250	2,500,000	E-2, St-14, P-32, L-52
	7/22/46	55	21,000	3,325,000	

Exudates—7/ 9/46 Smear from pus from abscess negative for organisms.
7/11/46 Culture of pus from abscess, *Bacillus coli.*

AUTOPSY REPORT

Clinical Diagnosis— Acute miliary tuberculosis
Prematurity
Bronchopneumonia
Gastroenteritis, due to unknown cause
Anemia of prematurity
Furunculosis.

Gross Anatomical Diagnosis.—
Purulent bronchopneumonia
Cerebral edema and hyperemia.

This was the body of an emaciated Negro female infant, 47 cm. long. The arms and legs were very thin. The pupils were round and even, being 4 mm. in

diameter. There was a clear fluid exuding from mouth and nose. No abnormalities of development were noted. The abdomen was greatly distended and tympanitic. The external genitalia were those of an infant female.

Peritoneal Cavity: The intestines were greatly distended with air. The viscera had its normal relationship. The liver was slightly below the right costal margin. The diaphragm was at the fifth rib, bilaterally.

Pleural Cavity: The lungs were voluminous, with smooth glistening surfaces. No adhesions were noted.

Pericardial Cavity: The surfaces were smooth and glistening, with a few cubic centimeters of dark yellow fluid present.

Heart: The heart was normal in size, with small petechiae over the epicardial surface, especially around the coronary sulci. The myocardium was dark grayish brown, with increased fragility. The foramen ovale was anatomically patent, but physiologically closed. The ductus arteriosus was only a strand.

Lungs: Both were well filled with air, having a light pink color. On section the bronchi were filled with a light yellow puslike material that may or may not be purulent material. There did not appear to be a great deal of increased peribronchial fibrosis. The substance was pink, moist, and had a bloody fluid oozing on the cut surface.

Liver: Appeared slightly enlarged with rounded edges. The substance had a dark reddish brown color with green mottling. These small green areas on the cut surface appeared to be especially prominent in the central zone of the lobules. The gall bladder and common duct were natural.

Spleen: The spleen was normal size, having a deep brown color with the lymphoid bodies readily seen.

Adrenals: Did not appear significant.

Kidneys: Both were of normal size, showing markedly a fetal lobulation. The bladder and ureters were normal.

Gastrointestinal Tract: The bowels were distended with air. The stomach and small intestines contained undigested and clear watery fluid. There were numerous petechial hemorrhages within the mucosal wall. The fluid of the lower intestines and colon took on a hemorrhagic tint.

Brain: There were numerous small areas of hemorrhage beneath the raised scalp. The tentorium cerebelli was a deep purple with small hemorrhagic areas over it and adhesive bands with the overlying brain tissue. Several small lacerations were seen. The configuration of the cerebrum was flattened and edematous, with the vessels being engorged. Several small hemorrhages were noted. An especially marked area of engorgement was seen over the cerebellum with a large hemorrhage over its left pole.

Microscopic.—

Heart: Pericardium, endocardium, and myocardium were negative.

Lungs: Areas of the lung showed multiple tubercle formations. In the center of these tubercles there were pyknotic nuclei and hyaline caseation. Around these centers were epithelioid cells. The cellular reaction around the tubercle was mostly monocytic, but lymphocytes and a few neutrophiles were seen. Occasional giant cells were present. The picture was suggestive of active tuberculosis. Acid-fast stains were positive for acid-fast bacilli.

Liver: A few small areas of focal necrosis were seen. The Kupffer cells of the sinusoids were loaded with red cells.

Small Intestine: Negative.

Spleen: The section showed two tubercle-like lesions. One consisted of a central area of acute inflammatory cells surrounded by epithelioid cells; the other was a solid mass of epithelioid cells and monocytes. A giant cell was seen near its center.

Kidneys: Negative.

Microscopic Diagnosis: Active tuberculosis of lungs, spleen, and possibly liver.

Clinical Summary.—This patient was a premature infant born at the seventh month of pregnancy. She cried immediately after birth and was brought to the hospital at once. She was a small child, and was given oral plasma, water, and Dextri-Maltose. A small abscessed area on the right thigh was noted, opened, and drained. On July 23, 1946, the abdomen became distended and soda enema was given. She died the following night at 7:55 P.M.

(We wish to express our thanks to Drs. J. A. Cunningham and L. C. Posey for doing the necropsy.)

CASE 2.—M. E. B. was the mother of B. G. B. This 19-year-old Negro primipara was admitted to the hospital on June 25, 1946, with complaint of chills, fever, and foul vaginal discharge. Sixteen days prior to admission she was delivered of a premature infant by precipitation. Post-partum convalescence was uneventful except for a bloody discharge until four days prior to admission. At that time she began to have backache, headache, chills, and fever, and the vaginal discharge became yellow and foul smelling. At the onset of these symptoms she was seen by a physician who gave oral penicillin without results. She was sent to the hospital for diagnosis and treatment.

Past History.—The past history was negative except for a positive Wassermann found in prenatal clinic. A presumptive diagnosis of syphilis was made and she was treated in the Anti-Luetic Out Clinic. The family history was negative.

A review of systems revealed poor appetite but no nausea or vomiting, no cough or chest pain. There was no bowel disturbance and no urinary difficulty.

Physical Examination.—Temperature 104.6° F., pulse 120, respiration 20, blood pressure 120/70. An undernourished, underdeveloped, Negro female, lying quietly in bed not appearing acutely ill. Eye, ear, nose, and throat examination was negative. Chest was clear to percussion and auscultation. Heart rate and rhythm were regular. No murmurs or enlargement were noted. The abdomen revealed no tenderness or masses. Pelvic examination revealed a foul discharge but no other pathology.

Clinical Course.—The clinical course was marked by daily spiking fever from 104° to 105° F. Treatment was symptomatic and supportive. She was given 25,000 units of penicillin, intramuscularly, every three hours for 1,000,000 units, without apparent result. An x-ray of the chest on the sixth hospital day was reported: "Extensive generalized miliary pulmonary infiltration, compatible with acute miliary tuberculosis." A Mantoux test on July 4, 1946, was negative. A check plate of the chest two weeks after the first showed extension of the miliary process.

The patient continued gradually downhill with daily spiking fever, and expired on the twenty-first hospital day. Permission for autopsy was refused.

LABORATORY REPORT

Urine.—Catheterized specimen on admission showed two plus albumin, one plus pus and an occasional cast.

Blood.—6/25/46 Hgb. 60 per cent, R. B. C. 3,250,000, W. B. C. 5,500, P-60, J-15, L-25.

6/25/46 Smear for cell pathology, anisocytosis, poikilocytosis, and central achromia.

Sputum.—Sputum was negative for tuberculosis on four occasions. Sedimentation rate corrected was 37 mm. per hour.

Blood Chemistry.—Blood sugar 70 mg., nonprotein nitrogen 19 mg., creatine 0.8 mg.

COMMENT

We feel that this case represents true transplacental transmission of tuberculosis, since the mother was a young Negress who, before delivery, and for a period of about two weeks post partum, had no history or findings suggestive of tuberculosis; and who even during her final illness had a negative Mantoux and negative sputum on repeated examinations, but during her last illness presented a characteristic chest x-ray and clinical picture of acute fulminating miliary tuberculosis. The rapidity with which the disease disseminated in the mother explains her lack of reaction to the intradermal injection of tuberculin.

The contact between mother and baby was minimal and besides this, miliary tuberculosis is considered to be noncontagious.

Most case reports of congenital tuberculosis are on mothers who were in advanced stages of the disease of the "adult" or open type, and many of the cases of tuberculosis in the offspring were due to infection at the time of birth from aspiration of infected material in the birth canal at the time of delivery.

SUMMARY

1. A brief review of the literature on congenital tuberculosis is presented.
2. One case of transplacental transmission of tuberculosis is reported.

CONCLUSIONS

It is suggested that the following definition be accepted generally for congenital tuberculosis: "Tuberculosis in which the infection occurs before birth by way of the blood stream, or by aspiration or ingestion of infected amniotic fluid in utero," and that all cases occurring at birth by the aspiration of infected amniotic fluid or tuberculous material present in the birth canal be classified as "tuberculosis neonatorum."

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CEREBELLAR MEDULLOBLASTOMA IN A SEVEN-MONTH-OLD INFANT

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ATTENTION is called to this case because of the early age at which cerebellar medulloblastoma was seen. The term medulloblastoma was first used by Bailey and Cushing[1] in a classification of gliomas on a histogenetic basis. The undifferentiated cell seen in this type of tumor, first described by Schaper in a series of papers from 1894 to 1897, was named "medulloblast" by Bailey and Cushing.

From a study of human embryos, Kershman[2] found that the medulloblast is a cell peculiar to the developing cerebellar cortex, in keeping with the observation that medulloblastomas occur exclusively in the cerebellum. With the cell found in the developing cortex, an early age incidence of medulloblastomas would seem likely.

Classification of medulloblastoma is criticized by Stevenson and Echlin,[3] who believe that some should be termed "granuloblastomas" since they are derived from the granular layers of the cerebellum. Of thirty-nine cases of medulloblastoma reported by Cushing[4] from 1913 to 1926, twenty-four were in patients under 15 years of age with an average age incidence at 10 years. In Cushing's report in 1930[5] of sixty-one cases, the youngest patient was 2 years of age, but had had symptoms for nine months. Among 4,563 necropsy records reported in 1923 by Wollstein and Bartlett,[6] there were five cerebellar neoplasms. A diagnosis of glioma (astrocytoma) was made in these patients with ages 2 years, 3 years, 17 months, 16 months, and 13 months, respectively.

Marion's case[7] of a 16-month-old male with a tumor in the region of the thalamus was reported to be a glioma.

Ford and Firor[8] reported a case of an invasive tumor covering the base of the brain and extending into the fourth ventricle in a 15-month-old male. The tumor was composed of irregular, spindle-shaped cells with scanty cytoplasm and definite glia fibrils.

Canavan and Hemsath[9] described a small body made up of ependymal cells in the floor of the fourth ventricle of a premature infant who died a few hours after birth.

Cases of teratomas, cysts of the choroid plexus, tumors of the pineal region, sarcomas, ependymomas, and papillomas have been reported in very young infants.

Gross[10] reported an 11-month-old male with symptoms since 10 months of age, who had a cerebellar tumor closely resembling a medulloblastoma. Gross also reported two other patients with conditions diagnosed as medulloblastoma; the patients were 17 and 19 months old, respectively. The average age of twenty-five patients reported by the Association for Research in Nervous and Mental Diseases[11] in 1937, was 19 years; the youngest patient was 4 years and the oldest 50 years of age.

CASE REPORT

A 7-month-old white male was admitted to the Babies and Childrens Hospital of Cleveland with the chief complaint of irritability, left facial paralysis, and turning of the head to the left. Birth history was normal and family history was noncontributory. He had been a healthy, normally developing infant until 6 months of age, when he began holding his head to the left side. From that time the infant had vomited projectilely about once a

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day. The vomitus did not contain bile. At 6½ months of age a gradually increasing left facial paralysis was noted, together with general irritability. There had been no significant fever. The mental development to the time of onset of his illness had been normal.

Findings at physical examination on admission were: temperature, 37.6° C.; weight, 7,010 Gm.; head, 44 cm.; chest, 42 cm.; a very irritable 7-month-old white male, head held to the left side with rotation of 45 degrees to that side. The infant tended to assume an opisthotonic position. The anterior fontanel bulged slightly and was quite tense. There was marked weakness of left facial muscles (seventh nerve) with diminished sensation on that side (fifth nerve). Pupils were equal and regular, and reacted to light. A weakness of the left external rectus muscle (sixth nerve) was noted. The left corneal reflex was diminished (fifth nerve). Fundi: papilledema was moderate bilaterally but somewhat more marked on the left. Marked resistance was observed to anterior flexion of the neck. The tongue was deviated to the right (twelfth nerve), and the gag reflex (ninth nerve) was questionably diminished. The uvula did not deviate. All deep tendon reflexes were hyperactive.

A lumbar puncture was done with caution to avoid possible herniation of the brain stem into the foramen magnum. Spinal fluid was slightly xanthrochromic under increased pressure (470 mm.) with 120 lymphocytes and 2 polymorphonuclears. Sugar and chlorides were normal. Admission chest film was interpreted to show a bronchopneumonia in the right hilus. There was no significant change in this film one month after admission. Skull films were normal at admission. Penicillin, intramuscularly, was given for the first hospital days to avoid intercurrent infection and also on the basis of the initial chest film.

It was felt that there was a space-occupying lesion of the left cerebellopontine angle which was increasing in size and was subject to hemorrhage. On the second hospital day a spinal fluid contained 1,650 fresh red blood cells per cubic millimeter, 11 polymorphonuclears, 30 small monocytes, and 45 small basophilic cells. These cells were in "clusters with irregular nuclei and were not inconsistent in size and shape with those found in a medulloblastoma," according to Dr. H. Z. Lund, pathologist. A subsequent spinal fluid specimen showed these cells, while ventricular fluid did not.

At this time Dr. C. S. Beck recommended x-ray therapy in view of the location of the tumor, presence of fever, and age of the infant.

On the fifth hospital day burr holes were made and repeated ventricular taps were made to relieve the increasing intracranial pressure until the twenty-sixth hospital day. X-ray therapy from the fifth to the thirty-first hospital day consisted of a total of 2,000 R. to the left occipital and 1,500 R. to the right occipital regions. At the end of this course of therapy there was considerable skin reaction in the occipital region which delayed operation until the fifty-third hospital day.

During the course of x-ray therapy when the infant was also receiving ventricular taps (in the beginning twice a day) the temperature fell from 39 to 40° C. to normal, irritability decreased as did the vomiting. There was no progression or regression of cranial nerve findings. After the course of x-ray, the infant's general course was downhill until the time of operation.

At operation, performed by Dr. Beck, the right cerebellar lobe was found to be displaced to the right with a cyst of the vermis containing about 30 c.c. of yellow fluid. The cyst extended laterally on the left, extending into the left cerebellar hemisphere and between the hemisphere and brain stem. The wall was very necrotic; part of the roof of the cyst was removed for study while about 15 c.c. of remaining necrotic material was removed.

For a few days following operation the infant did well, but in a short time his condition became critical and he expired on the tenth postoperative day (sixty-third hospital day). At this time measurements were: head, 46.5 cm.; chest, 36.5 cm.

Pathologic diagnosis of the surgical specimen was "necrotic tumor of cerebellum probably glioblastoma multiforme" according to Dr. H. T. Karsner.

It was felt that accurate diagnosis could not be made, due to the extensive necrosis of the specimen probably as a result of x-ray treatment.

Permission was obtained to remove the brain post mortem through the surgical incision. Microscopic diagnosis of this specimen was consistent with the early clinical impression of cerebellar medulloblastoma.

The tumor was large, necrotic, invasive, malignant, and tended to spread along the pia arachnoid and ependyma. The cells were rather small, somewhat ovoid, having scant cytoplasm and comparatively large, dark-staining nuclei, some of which were round and vesicular, others lobulated, and still others hyperchromatic. Mitoses were frequent. There were abundant vascular channels, many of which were thick-walled arterioles. The tumor cells formed clusters and collars about these vessels giving the so-called "pseudo-rosette" appearance. The tumor was mostly in the pia and arachnoid, and extended for a considerable distance in these linings. The underlying cerebellar tissue in some portions was not unusual, while in other areas there was invasion necrosis, focal hemorrhage, edema, and atrophy. There was marked necrosis in some portions of the tumor. The stroma of the tumor was scant and consisted mainly of pink-staining collagen material.

Interesting features of this case were the occurrence of a cerebellar medulloblastoma in a 7-month-old infant with the tentative diagnosis of the type of tumor made from the examination of the spinal fluid.

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Erratum

In the article by Cohen and Schneck entitled "Natural Incidence of Influenza Antibodies in Children of Different Age Groups" appearing in the February, 1948, issue of the JOURNAL, two paragraphs were moved in type by error. The first two paragraphs on page 159 should follow the first paragraph after Table II on page 156.

Psychologic Aspects of Pediatrics

THE CHILD WITH ASTHMA

RUTH MORRIS BAKWIN, M.D., AND HARRY BAKWIN, M.D.
NEW YORK, N. Y.

IT is unfortunate that a state of mutual suspicion and reluctance to accept each other's role in the study of allergic conditions so frequently exists between the pediatrician interested in allergy and the psychiatrist. Both should be concerned only with the lessons which can be learned through a cooperative, objective study of the conditions which have not responded to ordinary methods of diagnosis and treatment."*

The importance of psychologic factors in the pathogenesis of asthma has been recognized since antiquity. This viewpoint was accepted without question until the early years of this century. Since then attention has been directed toward the allergic component. Within recent years interest in the psychologic aspects of the problem has been revived and a fuller understanding of the interplay between tahe different mechanisms in the etiology of this harassing disease is being developed.[1]

The role of the emotions in precipitating the initial and also subsequent attacks of asthma has been stressed by McDermott and Cobb[2] and by Rogerson, Hardcastle, and Duguid.[3] McDermott and Cobb were able to elicit a convincing history of emotional factors in thirty out of fifty adults with asthma. Seven others were less convincing but strongly suggestive. They felt that, had more time been spent with each patient, psychologic factors would have been found in more cases. Twenty of their patients reported that the first attack was precipitated by an emotional disturbance.

In both adults and children the situations which most commonly induce an asthmatic attack are threatened separation from the mother, rage, and fear.[4] It is a not uncommon experience to have a mother report that she is afraid to cross her child lest he have an attack, and that the child's attacks are increased under emotional strain.

The importance of suppressed emotion in precipitating an attack of asthma and the subsidence of the attack coincident with release of tension were mentioned by Salter[5] in 1882, and this observation has been confirmed by many others since then. Salter states that, "The cure of asthma by sudden alarm takes no time. It is instantaneous. The intensest paroxysm ceases on the instant." He cites the history of a patient who was riding to the city to procure medicine to relieve the attack of asthma from which he was suffering. The patient rode slowly since he feared that exercise would exaggerate his symptoms. His horse ran away, and he was surprised to find that his symptoms had subsided completely.

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*Jensen, R. A., and Stoesser, A. V.: Emotional Factors in Bronchial Asthma in Children, Am. J. Dis. Child. 62: 80, 1941.

Lane,[6] in an account of her own symptoms, mentions that during adolescence, when she had many episodes of weeping, the number of attacks of asthma was less, only to increase later on when she showed better "control." Dekker[7] writes of a man whose attack of asthma was abruptly terminated when he was frightened by discovering that a Zeppelin was passing over his house. McDermott and Cobb[2] tell of a woman whose attacks of asthma became worse when she was annoyed by her husband. However, if she became very angry with him and flew into a rage the attack disappeared entirely at once. They suggest, as a possible explanation for the relief of an attack of asthma by strong emotion, the known beneficial effects of epinephrine on attacks of asthma and Cannon's work on epinephrine and the emotions.

The mothers of children with asthma show certain traits and attitudes with great uniformity.[8] They are usually the dominating force in the home, the fathers being passive. The mothers have been characterized as narcissistic, ambitious for themselves and their children, critical of their husbands, efficient, often earning more to support the family than do their husbands. They show little affection toward husband and children but are conscientious in their duties toward home and family. The children sense the lack of maternal affection and are disturbed accordingly. There may be intense sibling rivalry, sometimes to an extreme degree.

Parental overanxiety is the rule. The parents fear that an attack may be brought on not only by external factors and food indiscretions but by friction at home. They fear night attacks especially. The child himself becomes apprehensive and overanxious, and poor sleeping habits, restlessness, hyperactivity, and distractibility are the result.

The child with asthma has been described as irritable, aggressive, quick to respond, overanxious, and lacking in self-confidence.[9] According to Balyeat[10] and Rogerson and associates[3] the children with allergy are brighter than average. This has not been the experience of Piness, Miller and Sullivan[11] who reported the median intelligence quotient of 145 asthma patients to be 103 as compared with 105 for a group of Los Angeles school children selected at random. Children with asthma appear superior because their physical activities are restricted and they are kept indoors in association with adults, from whom they acquire good vocabularies and grown-up attitudes.

The behavior of the child with asthma is characterized by hyperirritability, overactivity, poor sleep, unreasonableness, and temper tantrums. These conduct disturbances are exaggerated before an attack, and improvement in behavior is often coincident with a decrease in the frequency and intensity of the attacks.

The relationship between the mother and the child with asthma is usually abnormally close. The child is overprotected, and his activities are limited as with chronically ill children in general. He is confined to the house unduly, his diet is restricted, and he is shielded from overexcitement. There may be considerable coddling to make up for these deprivations, and the child is pampered and coaxed and bribed to conform to the parents' desires. Health becomes all important.

Most children adjust to this close relationship with the mother by accepting her authority and relying on her to an abnormal degree. They find it difficult to make decisions and, when faced with new situations, an attack of asthma may result. On the other hand, a few children resent parental coddling and restrictions and become antagonistic, disobedient, and resentful. They are fidgety, destructive, and poorly disciplined. They often make poor adjustments in school.

In some instances the child does well when separated from the mother. Freedom from restrictions, free play with other children, and, most of all, separation from the tensions in the home seem to have a beneficial effect. There are less emotional upsets and, consequently, fewer attacks of asthma. Removal from the home is beneficial, probably, not only because of separation from the allergens but because of the substitution of a stable, emotionally healthy environment for the highly charged atmosphere of the home.

Retardation in schoolwork is common and has been considered to be due to frequent absences from school. The child may be placed in a class with younger children, which makes social adjustment difficult. A certain number of children with asthma have a specific reading difficulty. Though this does not appear to be more frequent than in school children in general, it usually goes unrecognized since the reading disability is attributed to the numerous absences from school.

The personality and behavior problems of the child with asthma are understandable as reactions to the parental personalities and attitudes. It is to be expected that the child will react to parental overanxiety, oversolicitude and overindulgence with immature and demanding behavior.

It has been suggested that the behavior disturbances of some children with asthma may be accounted for by local edema within the cranial cavity.[12] The resulting increased pressure may cause headache, vomiting, and dizziness. The child with asthma becomes irritable and disagreeable during a seizure. When the offending agent is removed, the child's mental attitude returns to normal. Dees[13] observed electroencephalographic changes in a large number of children with asthma, which tended to become normal with control and improvement of the allergy.

The extent to which emotional factors influence the severity of the asthma varies considerably. In some children they dominate the picture; in others their influence is minimal. The relative importance is estimated on the basis of careful history-taking and clinical observation of the mother and child.

History-taking should include information on the relation of emotional episodes to the occurrence of an attack; the child's and the parents' attitude toward an attack; the interparental relationships and the personalities of the parents, especially the mother; the parental attitudes toward the child. with especial reference to oversolicitude, overindulgence, overanxiety, and rejection; the personality make-up of the child, especially as to anxiety, immaturity, dependence; the relation to the siblings; the amount and nature of restrictions on physical activity; the relation to school.

By way of management, an attempt should be made to free the mother of her anxiety by reassuring her as to the benign outcome of the attacks. The ill effects of overindulgence on the personality development of the child as well as on the frequency of attacks should be stressed. Free activity and a full diet should be permitted as far as is compatible with the child's health. Rigid supervision should be relaxed, and the child should be allowed to make decisions compatible with his developmental status. Regular attendance at school should be urged, and difficulties at school should be corrected by special training if necessary. An attempt should be made to relieve tensions in the home.

Where the emotional difficulties in the home are deep seated, the aid of a psychiatrist should be enlisted.

Attention to the emotional and situational problems of the child with asthma in no way precludes other forms of therapy.

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Comments on Current Literature

INTRAVENOUS ADMINISTRATION OF FAT

VARIOUS discussions of parenteral alimentation have stressed repeatedly the need for a more efficient means of meeting energy requirements. In summarizing studies on infant diarrhea, Gamble[1] has pointed out that "the infant's food provides only a small surplus of oxidizable substances above the requirements for energy expenditure needed for growth. Even a small reduction of uptake of these substances will therefore cause progressive depletion of the energy stores of the body." Data are presented which give these simple and evident physiologic propositions quantitative illustration. Taking into consideration the difficulties encountered in attempting to satisfy energy needs by parenteral route, Gamble concludes that "the great desideratum would seem to be fat in such form that it can be given parenterally," and expresses the hope that "current attempts to produce a preparation of fat which will serve this end will go forward successfully."

In a recent issue of the *British Medical Journal* (Jan. 3, 1948), Magee[2] reviews the subject of intravenous alimentation. He concludes that, despite major advances in this field, energy requirements cannot be met readily by the usual methods of parenteral therapy and that the energy problem is one of incorporating fat into the injections in usable form. Magee describes work by Ivy, the results of which were made available to him by personal communication. Ivy succeeded in preparing a stable emulsion with which he was able to keep dogs in nitrogen balance, constant weight, and good health for forty-two days by exclusive intravenous feeding. This emulsion is composed of refined butter oil, purified lecithin, a sorbitan wetting agent ("Span 20"), glucose, and sodium cholate. Details of preparation are given in Magee's article, which states that while it has not been possible as yet to prepare a fat emulsion satisfactory for human use, "the work of Ivy and his colleagues is an important step in that direction."

Of special interest in this connection is an article by Shafiroff and Frank[3] in *Science* (Nov. 14, 1947) entitled, "A Homogeneous Emulsion of Fat, Protein and Glucose for Intravenous Administration." In a brief descriptive review of the various types of emulsions, reference is made by these authors to the use of egg lecithin, soybean phosphatides, and other agents used as stabilizers in the emulsification and stabilization of fat. However, while such emulsions have been well tolerated in some cases, they have not proved uniformly dependable because of varying degrees of toxicity of the stabilizing agent. Other methods of stabilization, such as the use of hydrophilic colloids, were discarded experimentally because of the frequency of fatal embolism.

In the laboratory of experimental surgery at New York University College of Medicine, two satisfactory types of fat emulsion have been prepared, the first an emulsion of coconut oil and serum albumin which on homogenization yielded a highly stable preparation well tolerated intravenously; the second derived from glucose, protein, and a neutral saturated coconut oil which could be sterilized with safety. The basic proportions of these constituents are as follows: "one l. of 6 per cent infusion gelatin (Knox P-20), one l. of protein hydrolysate 5 per cent amino acid solution, 200 c.c. of 50 per cent glucose solution, and 100 grams of pure, refined, edible coconut oil.

"After thorough mechanical agitation, the mixture is put through the Logeman homogenizer, an instrument so constructed as to make possible sterilization of its working parts. After this procedure of emulsification and homogenization, the material is collected in sterile vacuum bottle dispensers without any other processing and stored in the refrigerator. Refrigeration converts the emulsion into a solid gel which can be restored to the liquid state by warming the dispensing flask in hot water. Refrigerated samples have maintained complete stability after two months' storage. Test samples of the *p*H of the emulsion averaged 6.5. The droplets were smaller in size than that of the canine erythrocyte and were comparable to that of the chylomicra. The concentrations of fat, protein, and glucose were approximately 5 per cent each and averaged 800 cal./l. The gelatin acted as a stabilizer, partially as a source of nutrient energy, and served to maintain colloid osmotic pressure."[3]

This emulsion was administered intravenously to seven dogs and to twelve hospital patients. Three patients in the postoperative period were maintained exclusively on this emulsion with satisfactory results. One malnourished patient received intravenously with benefit a total of 5,500 c.c. of the emulsion (approximately 200 Gm. of fat) over a period of eight days. No thromboselerotic changes were noted in the recipient vein, and the preparation was not irritating when infiltrated into the tissues. In dogs studied at varying intervals following the administration of this emulsion, no evidence of fatty degenerative changes was noted in liver, lung, brain, or other organs.

This brief report concerning the possible use of a homogeneous emulsion of fat, protein, and glucose for intravenous administration in human subjects offers promise of real advance in this important field. Clinicians will await with interest more detailed studies concerning utilization of fat administered in this manner and more extensive reports of clinical application.

RUSSELL J. BLATTNER.

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Communication

To the Editor:

The Hungarian Medical Trade Union desires to celebrate the centenary of the Liberty War by arranging a medical convention in Budapest between Sept. 4 and 12, 1948. In the course of this week, the Pediatric Section will organize an International Congress of Pediatrics.

Of the five days of the Congress, two will be devoted to plenary sessions of all the sections. On three days the following topics will be discussed: rheumatic fever, toxicosis, and social significance and results of pediatrics. Lectures on miscellaneous subjects will also be held.

All pediatricians interested in the Congress are invited to participate. Those who expect to attend the Congress should communicate with the Centenary Congress Committee, Bokay János u. 53, Budapest 8, Hungary. Those who wish to take part in the discussion of one of the main topics or to present a paper on another subject are requested to give the title and a short summary of their lecture.

PAUL KISS, M.D.
PETER V. VÉGHELYI, M.D.

News and Notes

The **American Board of Pediatrics** announces the following examinations for 1948:

Cleveland, April 23, 24, 25
Chicago, June 25, 26, 27
Seattle, September 10, 11, 12
Atlantic City, November 17, 18, 19

Including those who passed the examination in Philadelphia in January, 2,749 certificates have been issued by the Board. The first certificate was dated June 10, 1934.

The annual meeting of the **Society for Pediatric Research** will be held on May 4 and 5, 1948, at the Seaside Hotel, Atlantic City, New Jersey.

The incidence of the infectious diseases common to children was low in 1947 throughout the United States, according to figures for the year through the week ending December 27, appearing in the Public Health Reports. Some of the figures are as follows:

	1947	1946	5-YEAR MEDIAN 1942-1946
Diphtheria	12,511	16,194	15,559
Measles	215,719	662,972	602,085
Scarlet Fever	83,300	112,981	140,475
Poliomyelitis	10,808	25,264	13,734

Whooping cough had an increase in reported incidence with 153,805 cases against 100,212 in 1946 and a five-year median of 123,554. Measles was definitely on the increase during the last few weeks of the year.

The **U. S. Army Medical Corps** now has a number of positions open in Army hospitals in Germany and Austria which can be filled by physicians who have completed their formal board requirements (residence phase) but who need one or two years of practice limited to their specialty. As of Jan. 1, 1948, there were ten positions available in pediatrics. These hospitals are registered with the A. M. A., and vary in size from station hospitals of 150 beds to general hospitals with 1,000 beds. This training may be acceptable by the specialty board as part of the period usually required to be spent in limited practice and experience prior to admission for examination. Interested members of the medical profession who have completed the formal training requirements for certification in one of the special fields are eligible to apply for these positions.

The locations provide excellent facilities and equipment, a wealth of clinical material, and the services of visiting consultants who are outstanding specialists in the various fields of medical practice.

The applicant may avail himself of this training for periods of one, two, or three years. Those applicants who are selected and who hold reserve commissions in the Medical Corps, will usually be recalled to active duty in the highest grade attained prior to release from previous active service. Those who do not hold such reserve commissions will be tendered a reserve commission in the Medical Corps in keeping with their age, years of professional experience, and prior service in any branch of the Armed Forces. Prior military service is not required. Individuals who are members of the U. S. Naval Reserve must transfer to the Army Reserve before being called to active duty. Families of married applicants will be allowed to accompany them to the place of duty. Suitable quarters are available. Families of individuals who do not declare their desire to serve for periods to exceed one year cannot be transported at government expense.

Eligible physicians are invited to communicate with The Surgeon General, U. S. Army, Washington 25, D. C., for further information. Inquiries should include the following information: name, address, age, nationality, marital status, dependents with age of each, medical school and graduation date, internship and date, details of graduate training, specialty and geographic location desired, contemplated length of service, details of prior military service.

Public Law 365, passed in 1947, makes it now possible for civilian doctors to become commissioned officers in the regular Navy, provided they meet the professional and physical qualifications. This law is unique in that it does away with, for the first time, the age limitation of 32 years and permits doctors in civilian practice to enter the Navy and be commissioned with the rank up to and including Captain. The law considers all strata of the medical profession, as interns, former medical officers who have resigned, and practicing physicians.

Applicants must be citizens of the United States, graduates of a Class "A" medical school, and have served at least one year's internship in an approved hospital. Candidates will be judged on a number of qualifications, such as being a diplomate of a specialty board, teaching connections, number of years of professional practice, hospital or laboratory connections, and military service. The allocation of rank to successful candidates will depend upon their academic age, professional standing, and experience in the medical field. Successful candidates will then be integrated in line with medical officers of the regular Navy. This means that they will be eligible for promotion along with their fellow officers of equal rank.

Doctors interested in such a career should write to the Bureau of Naval Personnel, via the **Bureau of Medicine and Surgery, Navy Department**, Washington, D. C.

The **American Jewish Joint Distribution Committee**, 270 Madison Ave., New York, is in urgent need for certain medical personnel for work with the Jews in Europe. The following places must be filled to carry out their program: two qualified public health

physicians; six public health registered nurses, one chief nurse to organize programs; one health consultant capable of setting up training schools for practical nurses; two nurse educators to head these schools; three medical social workers; and two public health dentists. All personnel must enlist for eighteen months. A knowledge of Yiddish is necessary.

The **Société de Pédiatrie de Paris** will meet at 4:30 P.M. on the third Thursday of every month at the Hôpital des Enfants Malades, 149 rue de Sevres. The president is Dr. G. Heuyer, 1 avenue Emile Deschanel; the secretary is Dr. Maurice Lamy, 94 rue de Varenne.

Following is the condensed financial statement of the **Fifth International Pediatrics Congress:**

Receipts	
Subsidies from Pediatric organizations in U. S. A.	
American Academy of Pediatrics (U. S. Members only)	$18,855.00
American Medical Association (Pediatric Section)	3,000.00
American Pediatric Society	1,000.00
Society for Pediatric Research	75.00
Contributions from philanthropic foundations and individuals	40,075.00
Contributions from industry	60,100.00
Revenue from registration fees	55,005.00
Total receipts	$178,110.00
Expenses	
Subsidies to 107 foreign delegates	$97,061.21
Promotional expenses	2,244.64
Secretarial and office salaries	4,602.36
Printing, stationery, postage, telephone, cables	9,444.52
Badges	2,430.00
Rental of space	8,000.00
Translations and translation equipment	5,197.98
Exhibit (expenses other than rental)	10,452.92
Reception, teas, luncheon to official delegates	8,000.00
Banquet	16,000.00
Steamer excursion	5,118.84
Post-Congress tours	1,836.02
Miscellaneous expenses	7,721.01
	$178,110.00

The following were certified by the **American Board of Pediatrics** at the examination in Philadelphia, Jan. 9 to 11, 1948:

Dr. Kenneth M. Alford, 159 Bidwell Parkway, Buffalo, N. Y.
Dr. Edward Bailey, 166-19 89th Ave., Jamaica, N. Y.
Dr. Evelyn J. Basile, 20 8th Ave., Brooklyn, N. Y.
Dr. Marvin L. Blumberg, 65-60 Booth Street, Forest Hills, N. Y.
Dr. Benjamin Wells Bullen, Jr., 149 Field Point Road, Greenwich, Conn.
Dr. John A. Burke, 337 Appleton St., Boston, Mass.
Dr. Arthur Wayson Chung, 295 West 11th St., New York, N. Y.
Dr. Charles Louis Dimmler, Jr., 2940 Summit St., Oakland, Calif.
Dr. Emanuel Fletcher, 140-10 Franklin Ave., Flushing, N. Y.
Dr. Alfred Leonard Florman, 35-24 78th St., Jackson Heights, N. Y.
Dr. John E. Gainor, 3 Groesbeck Place, Delmar, N. Y.
Dr. I. Gershman, 343 Thayer St., Providence, R. I.
Dr. Harry Gibel, 1171 Eastern Parkway, Brooklyn, N. Y.
Dr. Arthur A. Goldfarb, 1150 Grand Concourse, New York, N. Y.
Dr. David McLean Greeley, Babies' Hospital, New York, N. Y.

Dr. Joseph A. Hesch, 5821 Beaumont, Philadelphia, Pa.
Dr. Deborah B. Kaplan, Beard Building, 3 Main Street, Cortland, N. Y.
Dr. Thomas T. Kochenderfer, 1451 DeKalb St., Norristown, Pa.
Dr. Ella Langer, 96 State St., Augusta, Maine
Dr. Marion McIlveen, 88 West Ridgewood Ave., Ridgewood, N. J.
Dr. Harry S. Mackler, 752 North Broad St., Elizabeth, N. J.
Dr. Hyman Merenstein, 1324 48th Street, Brooklyn, N. Y.
Dr. Julius Yoland Miller, 1874 Commonwealth Ave., Brighton, Mass.
Dr. Doris H. Milman, 126 Westminster Road, Brooklyn, N. Y.
Dr. Frederic Clifford Moll, 300 Longwood Ave., Boston, Mass.
Dr. Marguerite Mary Neylan, 482 Beacon St., Boston, Mass.
Dr. John Richard O'Connell, 27 Ludlow St., Yonkers, N. Y.
Dr. William Obrinsky, 50 West 96th St., New York, N. Y.
Dr. Faith Newbury Ogden, 6 Stevens St., Norwalk, Conn.
Dr. Pauline Owyang, The Commonwealth of Massachusetts, Department of Public Health, 8 Beacon St., Boston, Mass.
Dr. Archibald Hanes Pate, 403 Borden Building, Goldsboro, N. C.
Dr. R. William Provenzano, 520 Commonwealth Ave., Boston, Mass.
Dr. Josephine Perlingiero Randall, Univ. of Pennsylvania, 3600 Spruce St., Philadelphia, Pa.
Dr. Nathan Ravin, 1185 Grant Ave., New York, N. Y.
Dr. Thomas B. Re, 420 50th St., Brooklyn, N. Y.
Dr. Anthony Joseph Repici, 212 Haddon Ave., Haddonfield, N. J.
Dr. Frederick Newton Roberts, 418 East Genesee St., Syracuse, N. Y.
Dr. I. Winfield Scott, 3209 North Meridian St., Indianapolis, Ind.
Dr. Charles F. Shevlin, 167-05 Hillside Ave., Jamaica, N. Y.
Dr. Milton Singer, 69 East 76th St., New York, N. Y.
Dr. Alfred Benjamin Stein, 959 East 55th St., Chicago, Ill.
Dr. Norbert Paul Sullivan, 35-35 82nd St., Jackson Heights, N. Y.
Dr. Henri Temerson, 45 West 90th St., New York, N. Y.
Dr. Ralph A. Warwick, 3300 Federal St., Camden, N. J.
Dr. Donald Weisman, 1 Greenridge Ave., White Plains, N. Y.
Dr. Albert B. Weisz, 42 St. Nicholas Ave., Brooklyn, N. Y.
Dr. Lucy M. White, 245 Alexander St., Rochester, N. Y.
Dr. Armine Taylor Wilson, Alfred I. duPont Institute, Wilmington, Del.
Dr. Lee Winston, 1321 South 6th St., Philadelphia, Pa.
Dr. Alfred Yankauer, Jr., 33 Riverside Drive, New York, N. Y.
Dr. Hedwig Zweig, 167 East 82nd St., New York, N. Y.

Book Reviews

The Gifted Child Grows Up. L. M. Terman and M. H. Oden, Stanford, California, 1947, Stanford University Press, pp. 448. Price $6.00.

What will happen to the gifted child and the child prodigy when he grows up has always been an interesting question. Whether he will adjust to a happy, normal life or will tend to develop neuroses and psychoses under strain, is an important medical question. Will the child superior mentally maintain this superiority when he grows up, or will he fall into the average as far as accomplishments are concerned? Most of us are familiar with what has happened to certain individuals, but the whole cannot be generalized from the particular, and hence the importance of Dr. Terman's study.

To the older pediatricians the name and work of Dr. Terman is well known. To the younger group it may be necessary to explain that in 1925 Dr. Terman published a most interesting study of 1,000 gifted California children. A gifted child was defined as one with an I.Q. of 140 or above. To pediatricians the important finding at that time was that in physical development the gifted children were superior to the general child population.

Follow-up studies of the group were published in 1930, and in the present text Dr. Terman gives data on the group obtained in 1940 and in 1945, when the average age was approximately 35 years. The original group was expanded to 1,528 of whom sixty-one had died. Dr. Terman and his associates have kept in constant touch with the group over the years and secured data on 97.7 per cent of the living in 1940. Over 1,400 of the group were actively cooperating. These figures make it the most remarkable follow-up study we have even encountered. There are hundreds of interesting facts and figures in the book, of which we can present only a few.

Up to 1940 sixty-one had died, or 4.07 per cent. There were ten additional deaths by 1945, including five war deaths. The expectancy figure for the general white population for comparable age is 5.02 per cent. Only six deaths by suicide had occurred, which is below the general rate for age. The insanity rate for the gifted group was 0.91 per cent against an expectancy rate of 1.00 per cent in 1940, and 1.37 against 1.43 per cent in 1945. Most physicians would have expected a higher, rather than a lower, rate. Eighty per cent of the group reported themselves in satisfactory mental health and adjustment.

Educationally, as might be expected, the gifted group were far ahead of the general population. The age of high school and college graduation was at least a year below the California average. Ninety per cent of the men and 86 per cent of the women entered college, and approximately 70 per cent were graduated. Over half the men returned for some form of graduate education as engineering and medicine. The average college grade was high, but for one reason or another, 7.7 per cent of the men flunked out.

Using the Minnesota Occupational Scale for their occupations, 45.44 per cent of the men fall in Group I, professional, and 25.69 per cent in Group II, semiprofessional and highest business. There were 6.22 per cent in Group V, semiskilled and minor business. Of the men, 9.53 per cent became lawyers; 7.59 per cent, teachers; 6.77 per cent, engineers; and 6.08 per cent, physicians. Of the women, 5.4 per cent became teachers of college rank, and 21.1 per cent, teachers below the college level. Two hundred and ninety-nine of the 617 women in the group were employed full time, and 259 were housewives not gainfully employed.

As a whole the earning power of the gifted group was superior to that of college graduates in general of comparable age.

Politically about 20 per cent tended to the radical side, 50 per cent to the average, and 30 per cent to the conservative. There was only one professed "Communist."

By 1945 the proportion of the men and women in the gifted group who had married was definitely higher than the rate for California or the United States as a whole. On the other hand, the offspring rate was lower, with a mean of 1.52 for those married five years or more. By 1945, 14.4 per cent of the men and 16.3 per cent of the women had been divorced or separated. Seventy per cent of these had remarried. The mean I.Q. of 384 offspring given the Stanford-Binet test was 127.7, or decidedly lower than the mean of the gifted parents. However, the number with an I.Q. of 150 or higher was twenty-eight times that for unselected children, upon whom the test is based. The mortality rate for the offspring was very low.

From the study the conclusion can be drawn that the average gifted child by the time he or she reaches 35 years of age has done very well. He is married, happy, physically and mentally sound, and well adjusted to his environment. There is, however, no evidence that the group as a whole has developed outstanding position or leadership. It will be most interesting to find out what has happened at the 45-year age level, as by that time the position and place in life of the individual is pretty definitely fixed. The one striking difference between the gifted group and the general average of human beings at the age of 35 is in the amount of college and university education they have received, and the high percentage in the various professions. This could have been expected, as the very basis of the group—superior intellectual capacity—would lead to intellectual interests and this in turn to the professions as an occupation.

B. S. V.

Traité de Diététique du Nourrisson. Maurice Lust, Paris, 1947, Masson et Cie., pp. 539. Price 1,000 francs.

In this text Dr. Lust, chief of the Center for Puericulture in Brussels, has assembled an encyclopedic volume on infant nutrition and feeding. There are well over 1,000 references to the literature assembled in the bibliography, including those of 1946, and if the references to the work in other countries are as complete as the knowledge and inclusion of the American work and literature on the subject, there has been very little omitted. The text contains a discussion of maternal and artificial feeding, modified milks, feeding without milk, weaning, and the feeding and nutrition of the premature infant. It is not a text for the student or practitioner, as all the conflicting ideas and thoughts on infant nutrition are presented, but it should be a valuable reference book for pediatric departments for its monumental discussion of the subject and its presentation of the thought and work on infant feeding throughout the world.

Editor's Column

SCHOOL ACCELERATION

Whether or not the child with superior intellectual endowment should be accelerated in the grade and high school is a moot question in education. Some educators feel that the child's position in school should correspond with his intellectual ability and development so that he will not become idle or bored with his studies, which at times leads to poor work. Others contend that acceleration leads to social maladjustment which is even worse for the child's development, and hence he should be kept closely to the chronologic average. This group advocates compensating for the intellectual superiority by adding interesting intellectual activities to the regular curriculum for the age. Many times the advice of the family doctor is sought when the question of acceleration is being discussed.

In his book on *The Gifted Child,* which is reviewed on page 330 in this issue, Dr. Terman devotes a chapter to the subject, based on the data of his group, of whom a large percentage graduated from high school a year younger than the average, and between 25 and 30 per cent around two years or more. Dr. Terman believes the risk of maladjustment is less than commonly believed. He considers that the disadvantages of acceleration which were so frequently mentioned in his study are usually temporary, and in his opinion children with an I.Q. of 135 or above should be promoted sufficiently to permit college entrance by the age of 17.

The physician is interested in the normal growth and health of the child as a whole, which includes the physical and emotional development as well as the mental. Education is only a means to a goal and not a goal in itself. It is our feeling that the advice of the physician should be based very largely on the findings for the individual child in question. If, for example, the child is above the average in physical development for his age, and this is frequently the case with gifted children, there is far less danger of social maladjustment leading to unhappiness than if the child is below or even at the average development for his age.

The problem is not so important or pressing for girls, who mature two years earlier and whose growth problem is practically over by the latter part of the high school course, as it is for boys, who continue to grow up to the end of the high school years and even beyond. The matter of the past health record is of great importance. Certainly undersized and underdeveloped children or those whose health record is poor should not be placed in competition with children of older chronologic age, to balance a mental age parity.

It would be of great advantage for the gifted child to be accelerated in his grade and high school work if it were definitely known at this early age that the child would enter one of the professions, as medicine, which require years of graduate work. Such a choice or decision, however, is premature before the college years as a rule. However, as Dr. Terman shows in his book, the percentage of gifted children who enter the professions is much greater than the percentage of college graduates as a whole. A reduction in the years spent in grade and high school studies would be of great help in medical education.

B. S. V.